Management of Neuroendocrine Tumors of the GI Tract

Updated: August 2, 2004

Authors: Aaron Vinik, MD

Somatosatin in Treatment of Malignant Neuroendocrine Tumors

Somatostatin, a tetradecapeptide, is a small cyclic peptide. It circulates in the blood in two biologically active forms: somatostatin 14 and somatostatin 28 (429;430), processed from their precursor pre- and pre-pro-somatostatin molecules. Somatostatin inhibits the secretion and action of a number of peptide hormones, neurotransmitters, and exocrine secretions of the GEP axis. It also inhibits a variety of gastrointestinal functions including gastrointestinal motility, gastric acid production, pancreatic enzyme secretion bile secretion and colonic secretions. It inhibits secretion of a number of gastrointestinal and pancreatic hormones such as insulin, glucagon, pancreatic polypeptide, secretin and vasoactive intestinal polypeptide. In addition to it functions as a regulator of neurotransmission and gastric and intestinal hormone secretions, it may control cell proliferation in normal tissues and in tumors(429;431;432). Its clinical use is limited because of its short half-life of 1 to 2 minutes, the need to give it intravenously and the multifarious effects and the rebound of secretions when it was stopped (433). Development (433) of its potent, long-acting octapeptide analogue (Sandostatin, octreotide acetate) with a half-life of over 100 minutes was a breakthrough for clinical application. Other analogues such as somatuline (BIM 23014 C) are being investigated. Thus far, their effectiveness and toxicity rates appear to be similar to those of octreotide. Several aspects of treatment of GEP neoplasms, including symptom reduction, hormone suppression, tumor growth, and survival, are discussed here.

Somatostatin receptor subtypes

Somatostatin-14 and somatostatin 28 act through high affinity G protein coupled membrane receptors. Five somatostatin receptor (SST) subtype genes have been cloned and characterized, SST1-5 (434) and are localized on different chromosomes (435). Two forms of the SST2 (a and b) are generated through alternative splicing (436), (435). A number of systems are activated after binding to the respective receptors: 1. inhibition of adenylate cyclase; 2. inhibition of calcium channels; 3. stimulation of phosphotyrosine phosphatase; 4. inhibition of MAP kinase activity(437), (435;438). The effects on adenylate cyclase and calcium

channels are important for hormone and intestinal secretion and those on the phosphotyrosine and MAP kinases for cell growth and proliferation (431;432).

Somatostatin target tissues express multiple SST subtypes although individual tissues may express different subtype uniquely. Pancreatic islet cells express all five SSTs (439;440). However in these cells the SST 1, 2 and 5 subtypes are the most abundant with pancreatic b cells expressing predominantly SST1 and 5, and a cells expressing SST2, δ cells SST 5(440).

Tumors arising from somatostatin target tissues often express a high density of SSTs.(441-445). These tumors include pancreatic endocrine tumors, carcinoids, paragangliomas, pheochromocytomas, medullary carcinomas of the thyroid, in addition to pituitary prolactinomas and non endocrine tumors such as the breast and malignant lymphomas (441;446). This can be determined immunohistochemically or by in situ hybridization and RNAase protection assays and RT-PCR (143;447). The majority of these tumors express multiple subtypes of SSTs but there is considerable variation between subtypes expressed by different tumors of the same class, and even different metastases deriving from the same tumor (439;448-450). Endocrine pancreatic and gut tumors have SST2 more than 80% of the time (443;451-453).

The five subtype of SSTs bind somatostatin 14 and somatostatin 28 with high affinity. The SST4 however does not bind octapeptide analogues octreotide and lanreotide whereas the SST2, 3 and 5 display high, moderate and low affinity for these analogues. The predominant expression of SST by endocrine tumors of the pancreas and GI tract forms the basis of use of these analogues for the treatment of the expression of the endocrine tumor (454),(204) . The high density of the SST subtype in these tumors predicates the use of radiolabel analogs for the localization of tumors and their metastases and indeed is predictive of response to therapy, and parallels the presence of receptors identified immunochemically (147;455-459). This knowledge is important in deciding on the appropriate from of therapy.

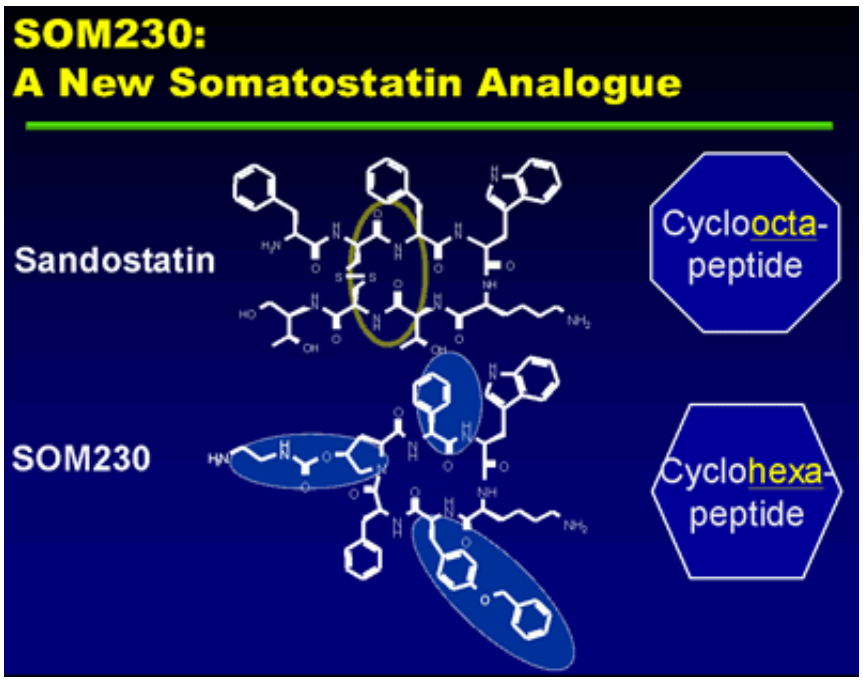

Figure 1

An interesting recent discovery is that the SST receptors may form heterodimers with other G protein coupled receptors such as the dopamine D2 and the u opiod receptor (MOR-12) resulting in a novel receptor state with properties different from the parent receptors (460;461). This predicts that future analogs may become hybrid molecules with the ability to bind and activate these hybrid receptors and expand the limited capability in certain tumors or even overcome the apparent tachyphyllaxis that seems to occur in many of the tumor syndromes.

Somatosatin Analogs

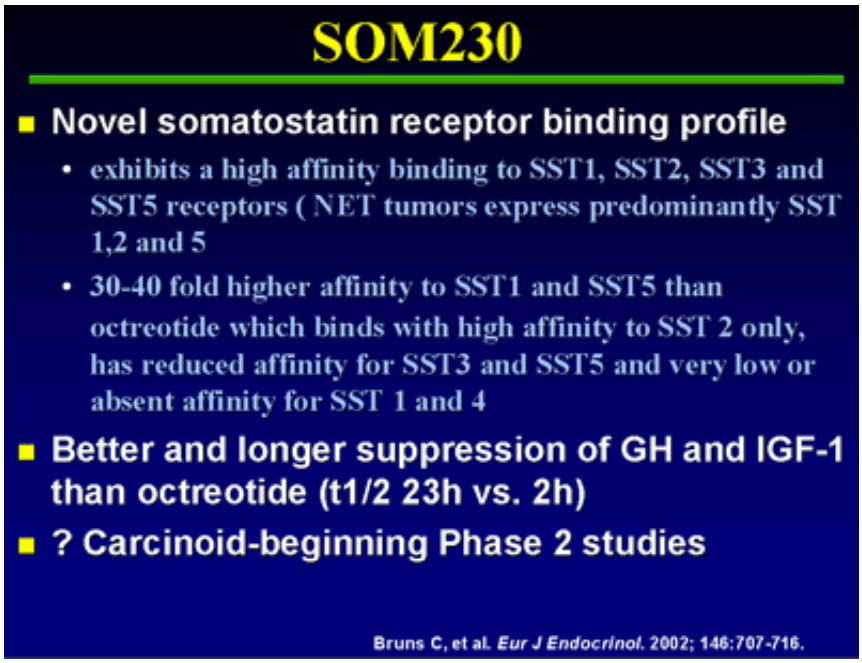

Figure 2

As discussed above the short half life, the tendency to rebound , the need to give somatostatin intravenously by infusion, created the need for synthesis of analogs with longer half lives which could by administered by routes other than IV and that suppressed secretions for protracted periods without a tendency to rebound. The first such analog was octreotide (Sandostatin, Novartis, Basel, Switzerland). Its elimination half life after SC administration is of the order of 2h and rebound hormone secretion dose not occur (462) Octreotide does not bind to all the SSTs but preferentially binds to SST2 and 5 with high affinity (438). Other cyclic analogs with almost similar affinity and specificity include lanreotide (Somatuline, Ipsen, Biotech, Paris, France) have subsequently been developed (433). The slow release deport intramuscular formulation of

octreotide (Sandostatin LAR, Novartis Pharma, Basel, Switzerland) has to be administered once every 4 weeks and lanreotide (Somatuline PR, Ipsen Biotech, Paris France) once every two weeks. A new slow release of Lanreotide, Lanreotide Autogel (Ipsen Biotech, Paris, France) has been introduced in Europe and can be given by deep subcutaneous injection every 4 weeks.

Symptom control with somatostatin

In most patients with carcinoid tumnors and pancreatic endocrine tumors treatment with octreotide induces a rapid clinical response in the symptotology such as diarrhea, dehydration, flushing attacks, hypokalemia, peptic ulceration and the necrotic skin lesions **.** Unfortunately many of these patients show desensitization of the inhibition of hormone secretion by octreotide within weeks to months. In a series of 57 patients with carcinoid, octreotide therapy was ended in 23 patients after periods ranging from 1 week to 12.5 months, median 4 months, whereas the remainder could be controlled for periods up to two and one half years. The estimated mean duration of response of the whole group was 1 year (463).These were early studies and no attempts were made to adjust dosage, use periods free from the analogs for reduction of tachyphyllaxis or give the agents by continuous infusion as has been shown to be successful in some recalcitrant cases and certainly is the best form of therapy for acromegaly (464). Potential mechanisms of the tachyphyllaxis and resistance to the action of somatostatin are :. receptor down regulation, a decrease in the number and affinity of the SSTs, desensitization due to uncoupling of the receptor from the G protein second messenger, differences in the degree and type of receptor expression in the tumor metastases, or even growth and development of clones resistant to the action of somatostatin, resistance of the target hormone secretory mechanisms to somatostatin or their growth promoting properties for these tumors e.g. growth hormine or gastrin, and finally mutations in the SST genes and their functional peptide receptors (465).

Somatostatin in Treatment of Malignant Neuroendocrine Tumors

Symptom Control

Octreotide has a potent action in reducing symptoms in certain neuroendocrine tumors. Detection of somatostatin receptors by octreotide scintigraphy correlates well with the predicted response to treatment with octreotide (155). In carcinoid tumor, flushing is reduced in most patients (205;206;466). The acute effects on water and electrolyte transport are a reversal from a secretory to an absorptive state, thus normalizing transport across the proximal intestine (204). Long-term responses of diarrhea, however, differ in different reports: 9 of 14 patients with endocrine diarrhea responded to treatment in one report,(211) in contrast to 19 of 25 in another (205). Diarrhea in VIPoma improves 95% of the time (466). This difference might result from the involvement of different peptides causing diarrhea and different mechanisms. In five of our patients with gastrinoma, the presenting symptom was diarrhea, which improved, as did 65% of 26 reported cases(466). Diarrhea in 16 patients with glucagonomas also improved uniformly (466;467). Diarrhea also improves in all patients with gastrinoma syndrome, and abdominal pain can be relieved in most patients (98). There is, however, the possibility of a rebound in symptoms and/or hormonal values during therapy. The mechanism of this is not clear, but it

might involve accelerated enzymatic breakdown of octreotide and/or ligand-induced changes of somatostatin receptors on the target cell, preventing internalization of the hormone receptor complexes or a gradual adaptation of the target cell to the octreotide effect, as proposed by Koelz and colleagues (468).

Wheezing, as one of the symptoms in carcinoid syndrome, can be reversed by octroetide, and spirometric improvement in lung function has been documented (211). In another patient who had severe proximal myopathic muscle weakness, clinical and electromyographic improvement occurred with octreotide treatment (211). The arthropathy of carcinoid, which may be SP mediated, also improves (389). Hypoglycemia with insulinoma responds erratically because of unpredictable effects on food absorption, suppression of glucagon, and insulin (204). Of 15 patients, 50% improved, and 30% got worse (466). The necrolytic migratory erythema of glucagonoma clears in only 50% of the cases. (469)

Hormone Suppression and Biochemical Features

Octreotide inhibits hormone secretion in some malignant GEP tumors. The most sensitive of these seems to be VIPoma, where lowering of VIP circulating levels parallels relief of symptoms (204;207). Gastrin levels, however, are not equivalently lowered with octreotide. One study of eight patients with gastrinoma showed that octreotide decreased gastrin levels in five patients by a mean of 76% of baseline (98). In worldwide pooled data (n = 26), 70% of patients are reported to respond. ACTH overproduction heralds unresponsiveness to the drug. Glucagon levels seldom decrease (466). Although the overall 5-HIAA level is significantly lower after octreotide treatment, (205) blood serotonin level does not differ significantly (206;470). There is an overall reduction of 5-HIAA in 58% of patients (466).

Perioperative Management

Carcinoid and other GEP tumors can be a major therapeutic problem perioperatively, when vast quantities of active peptides are released into the circulation from manipulation of the tumors. Octreotide is an effective suppressor of release and action of peptide hormones during surgery (278). Profound refractory hypotension in carcinoid syndrome can be rapidly reversed by octreotide, (203) as can gastric acid secretion and fistula drainage (278).

Tumor Growth

While expression of SSTs is essential for the control of hormone and intestinal secretions by somatostatin and its analogs, somatostatin has been shown to inhibit normal and tumor cell growth. Induction of G1 arrest and apoptosis has been demonstrated in a number of tumor cell models and involves a number of the SST receptor subtypes (471-473) , (474), (475-481). Reports of tumor regression or even infarction support the notion that somatostatin has antitumor activity aside from controlling secretions (482). Based upon clinical observations that administration of somatostatin during angiography of metastases to the liver, Cho and Vinik postulated that it had vasoconstrictive or anti-antigenic properties (483) and indeed it is now known that these drugs are anti-angiogenic in malignant vasculature, inhibiting vascular growth

factors and are anti apoptotic for malignant cells (484-492).

Somatostatin Scintigraphy

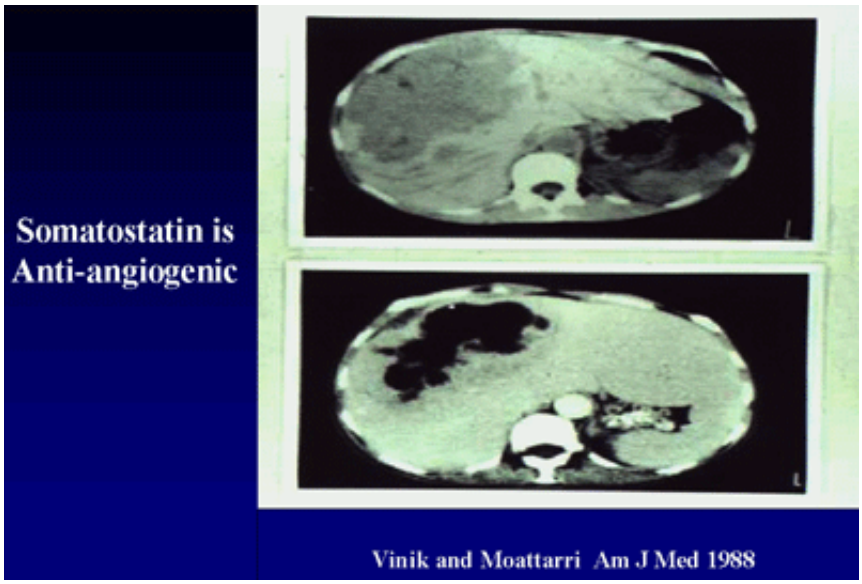

Figure 3

Tumors that have SST 2 or SST 5 receptors can be visualized in vivo after the injection of radiolabeled octapeptide analogs of somatostatin. The technique was first developed using the radiolabeled somatostatin analog 123I-Tyr3 octreotide (493). Unfortunately this analog was difficult to prepare, cost was prohibitive, it accumulated in the liver gallbladder and ducts and gastrointestinal tract forcing the development of newer and better analogs. The most widely used for SST scintigraphy is now ^{111} In-pentreotide (^{111} In-DTPA ^{0} octreotide, Octreoscan, Tyco Healthcare, Mallinckrodt, St Louis USA) **(146)** . Apart from ^{111} In-pentreotide, ^{111} In-DOTA ^{0} lanreotide can also be used (494;495). Of greatest importance in this regard is the fact that a negative scan predicts absence of the appropriate SSTs and does not augur well for a tumor response. In clinical practice a negative scan suggests that alternative therapies should be sought. It is the relationship between tumor mass identifiable on CT, MRI or even PRET and the concordance with the somatostatin scan that suggests that the tumor is indeed receptor positive and likely to respond. Dissociations between the Octreoscan and other modalities of imaging suggest that the tumor is devoid of the needed SSTs and will not respond. Thus clinical decision making is simplified by this approach (496).

Octreoscans may not be universally equivalent. Granberg et al(497) from the University Hospital in Uppsala identified 28 patients with histologically verified bronchial carcinoids and prospectively carried out Octreoscans and Ct Scans of the chest . Altogether 71% had octreoscan positive tumors. The primary tumor was positive in 13/16 whereas the CT was positive in 15/16. CT failed to localize the tumor in 1 octreoscan positive patient. Intrathoracic

metastases were visualized by Octreoscan in 7/9 patient and by CT in 8/9 patients. Of the liver metastases octreoscan was positive in 9/14 (64%) and of bone metastases it was positive in 9/10. The authors conclude that octreoscans are useful for following patients with bronchial carcinoids but that CTs are better for identifying the primary tumor as well as metastases to the liver.

Because GEP tumors grow slowly, it is hard to assess the effect of treatment on tumor growth. Long-term CT monitoring, however, has shown shrinkage of liver metastasis in certain patients with carcinoid and other GEP tumors (205;216). In 85 carcinoid tumors, no change was found with doses under 50 mg/d, but Kvols and colleagues [112] reported a decrease in size in 17% of patients using higher doses (1,500 mg/d). VIPoma, glucagonoma, and gastrinoma generally do not change in size (466), although a tumor infarction has occurred in VIPoma (278). Tumor metastases to bone may occur despite apparent control of the primary tumor or liver metastases (204;498).

Somatostatin Isotope Ablative Therapy

It might be feasible to use the peptide in both peptide therapy as well as in SST targeted radiotherapy. Once bound to its SST the agonist SST complex is internalized as are many G protein coupled complexes (465;499-503). The SST subtypes have a differential rate of internalization which may account for differences in the susceptibility of different tumors ion different target tissues. The SST1 show low agonist-induce internalization whereas the SST_2, SST_3, SST_4, and SST_5 are more efficient in this respect (438;465). When ^{111}In-DTPA ^{o} octreotide is administered to patients with carcinoid tumors it is taken up, bound to the plasma membrane, internalized and appears in the cytoplasm and in the cell adjacent to the nucleus. Proximity to the nucleus is important for this short range Auger electron emitting radioisotope to exert its cytotoxic effect(504). Thus the predominant expression of SST_2 receptors on these tumors and the avidity of this particular receptor for octreotide make it particularly suitable for application of SST targeted therapy. However, the Auger emitter ^{111}In has a low tissue penetration and stable a or b emitting isotopes could not be developed. As a result novel compounds were developed allowing the use of more powerful isotopes e.g. [DOTA ^{0}, Tyr 3] octreotide allowing stable binding with the b emitter yttrium 90 (Octreother, Novartis, Basel Switzerland). In addition ^{111}In-DOTA0] lanreotide and ^{90}Y-DOTA ^{0}] lanreotide can be used for advanced tumors containing the SST_2 and SST_5 receptors (450;505-509). While several mechanisms determine the efficacy of these radiotherapeutic drugs which are not unlike the biological effects of somatostatin analogs, there is the added need for stability of the radioligand, the density of SSTs on the tumor, the affinity for the ligand, the efficiency of internalization and the trapping of radioisotopes within the tumor cells, tumor and the mass of injected peptide(465;510;511).

Future Directions

Because of this unique aspect of these tumors and their tissue receptor expression and the selectivity of currently available analogs, it was expected that new analogs with different specificities and would be found that bound to SSTs other than SST2 and SST 5. A new- so called universal somatostatin analogue has been found and named SOM 230, which has high

affinity for SST $_{1,2,3 \text{ and } 5}$. It is currently being evaluated in phase 1-111 trials (512;513) and shows promise for acromegaly and the reduction of IGF-1 levels. New drugs with multi receptor binding capabilities and analogs that form homo or hetero dimmers may yet offer greater potential of uptake and internalization by these tumors. Possibly this will yield improved results in terms of desensitization (460;514;515). .Hybrid molecules, for example somatostatin –dopamine, have a high affinity for both somatostatin and dopamine D $_2$ receptors and may be particularly useful for prolactin secreting tumors. While this peptide radiotherapy seems exciting it has yet to fulfill its promise. In the USA today it is only available at select centers doing trials and has not yet been incorporated into any schems whereby patients with these tumors are being treated. Other alternative approaches such as gene therapy with targeted ablation of an SST subtype over-expressed on a tumor or induction of expression thereby increasing the likelihood of response to an analog are in the future.

It has recently become clear that endocrine cells are not the only tissues that express the SST receptors. There is now evidence that there is differential expression of SSTs on low and high grade astrocytomas (516) and although this did not show predictive value for survival time it does raise the possibility of developing a new therapy for this notoriously difficult tumor. Even in pancreatic cancer there appears to be a difference in the expression of SST2 in the cancer and its adjacent tissue, which might be reason for the differences in therapeutic effects of somatostatin on these cancers. Interestingly these tumors express DCP4, p53 and ras genes reciprocally with the SST2 receptor and may thus participate in pancreatic angiogenesis. (517) Analogs that target the SST2 receptor may compromise angiogenesis so essential for the growth and proliferation of these tumors. DOTA Tyr3-octreotide (DPTATOC) and DOTA 0 Tyr 3-octreotate, bound to beta emitting radioisotopes, are suitable for therapeutic use but this is still in the research arena. From the point of view of radiometabolic therapy directed towards the destruction of micro metastases, pharmacological research has provided a host of potential candidates : octreotide LAR, lanreotide, vapreotide, BIM-23244, BN 81644, PTR 3173, BIM 23A387, SOM-230 with different pharmacokinetic properties and receptor binding characteristics (518). The most developed of these is perhaps SOM 230. It is a cyclic hexapeptide which is metabolically stable and has a terminal half life in animals of 23h. It is about 40 times as potent as somatostatin in the inhibition of growth hormone and by continuous infusion causes 75% reduction in IGF-12 levels compared with 28% by somatostatin itself. It binds to the SST 1,2,3 and 5 receptor subtypes, but has less potency on insulin and glucagon secretion and does not alter glucose tolerance. It seems that it will be a useful analogue for acromegaly but the question of its added advantage in carcinoid and other tumors of the gastroenteropancreatic axis remain to be resolved .(512)

Is Lanreotide or Octreotide and/ or interferon Alfa an adequate therapy for neuroendocrine tumors?

Both somatostatin and its analogs as well as interferon alpha have been shown to control hormonally active functional neuroendocrine gastroenteropancreatic tumors. Faiss et al (519) carried out a prospective randomized multicenter trial on the anti-proliferative effects of lanreotide, interferon alpha and their combination for metastatic neuroendocrine tumors in 80 therapy naïve patients with histologically proven neuroendocrine tumors (primary location: foregut, n=36, midgut, n=30, hindgut, n=3, unknown, n=11, functional , n=29, non-functional,

n=51). Patients were randomly treated with lanreotide(1mg tid, SC) or interferon alpha (5X10-6 units tiw, SC) or the combination of the two. . All patients had disease progression prior to entry into the study verified by imaging studies. Twenty five patients were treated with lanreotide, 27 received interferon α and 28 patients received the combination. Partial tumor remission was seen in 4 patients , 1 on lanreotide, 1 interferon α and 2 patients who received the combination. During 12 months of therapy, stable disease was observed in 19 patients (7 on lanreotide, 7 on interferon α and 5 on the combination) whereas tumor progression occurred in 14/25 patients on lanreotide, 15/27 on interferon α and 14 on the combination. Side effects leading to interruption were more frequent in the combination group than either of the individual groups. The authors of the “International Lanreotide and Interferon Alfa Study Group (519) conclude that lanreotide and interferon α have comparable anti-proliferative effects in the treatment of metastatic neuroendocrine tumors of the Gastroenteropancreatic axis…

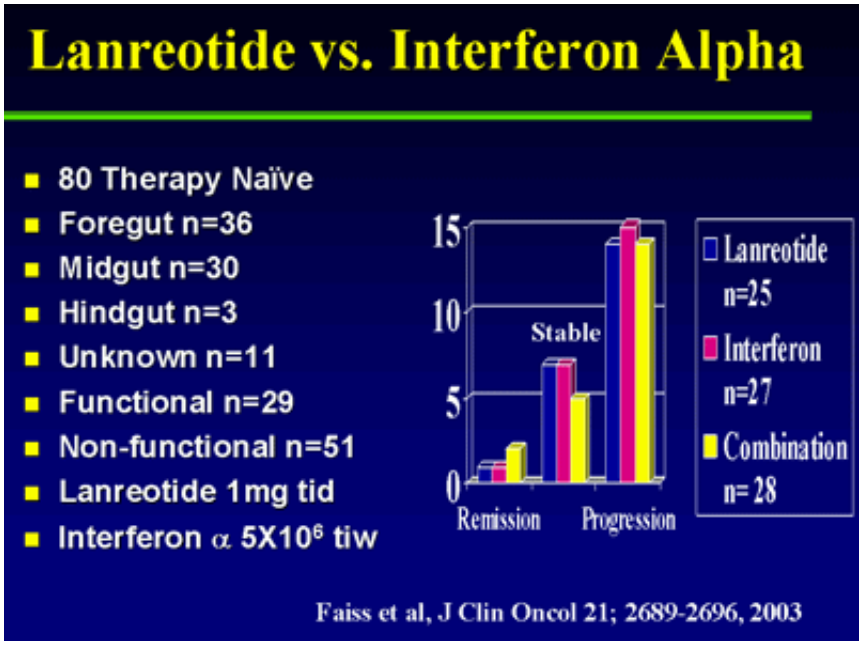

Figure 4

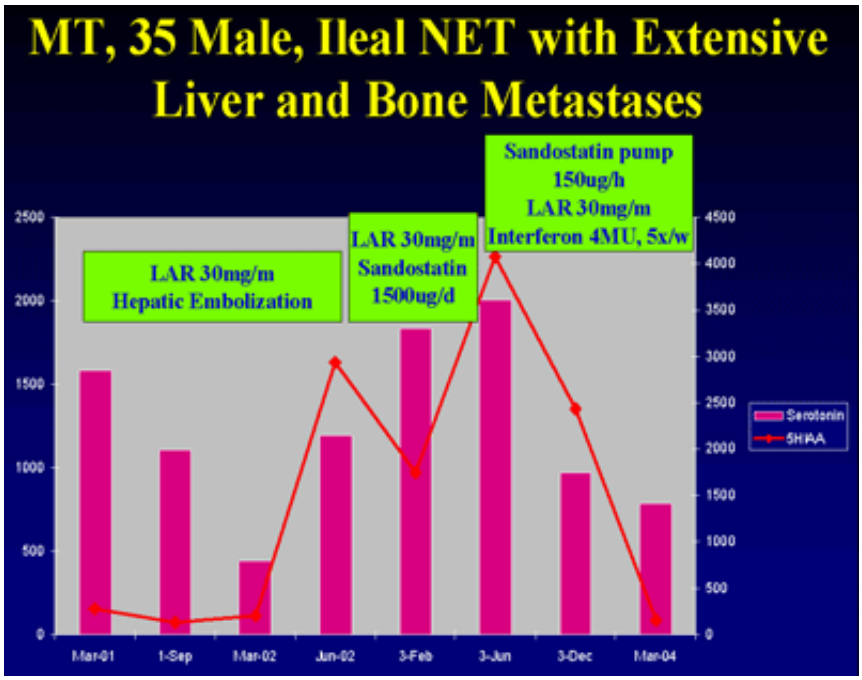

Figure 5

Response rates were however lower than those previously reported in non randomized studies and no attempts were made to escalate dosage or to deliver the somatostatin by continuous infusion. It would seem that the combination may yield slightly greater advantage. No attempt was made in the study to determine if those failing on lanreotide could be rescued with interferon. Similar results were found for the functional and non functional tumors but however there are very marked differences in clonal responsiveness and the presence or expression of SSTs, so the study fails to address the true response rate in receptor positive people and if dosage had been maximized. It nonetheless suggests that in the presence of failed optimized therapy with a somatostatin analogue there is room for the introduction of interferon and that the side effects are not. Figure 18 indicates just such an example. Patient MT had a very good response initially to LAR, 30 mg /day with a fall in serotonin values to near normal. However, over the next 9 months serotonin values began to rise and Sandostatin 1500ug/day was added to the LAR without much success. However the addition of Interferon alpha 4M units 5X/week caused a dramatic reduction in serotonin values. Cases such as these indicate that the use of Inteferon may represent a fall back position when one is losing ground with LAR and somatostatin.

Conclusions on the role of somatostatin in treatment of neuroendocrine tumors

The role of octreotide in the treatment of GEP tumors is still well established. Because of the clear evidence of symptomatic relief (e.g., flushing, wheezing, diarrhea), it has established a place in treatment of such tumors both pre- and postoperatively. Perioperative use can prevent fatal episodes of rapid, extreme increases of hormones in the circulation. There is enough

evidence for the control of tumor growth that primary treatment of select metastatic tumors, with proper monitoring of tumor growth, is recommended.

References

1. Pearse AJE. Common cytochemical and ultrastructural characterisiticsof cells producing polypeptide hormones(the APUD series. and their relevance to thyroid and ultimobranchial C cells and Calcitonin. Proc R Soc London B 1968; 170:71-70.

2. Andrew A. An experimental investigation into the possible neural crest origin of pancreatic APUD cells. J Embryol Exp Morph 1976; 35:577-570.

3. Le Douarin NM, Teillet MA. The migration of neural crest cells to the wall of the digestive tract in avian embryo. J Embryol Exp Morphol 30, 31. 1973.

4. Pictet RL, Rall LB, Phelps P, Rutter RJ. The neural crest and the origin of insulin-producing and other gastrointestinal hormone-producing cells. Science 1967; 191:191-190.

5. Guz Y, Nasir I, Teitelman G. Regeneration of Pancreatic B Cells from Intra-Islet Precursor Cells in an Experimental Model of Diabetes. Endocrinology 142, 4956-4968. 2001.

6. Pictet RL, Rutter WJ. Development of the embryonic endocrine pancreas. In: Steiner DF, Freinkel N, editors. Handbook of Physiology, Section 7: endocrinology, vol. 1. Washington,D.C: American Physiological Society, 1972: 25-66.

7. Pang K, Mukonoweshuro CH, Wong GG. Beta cells arise from glucose transporter type 2 (GLUT-2. -expressing epithelial cells of the developing rat pancreas. Proc Natl Acad Sci 91, 9559-9563. 1992.

8. Ramiya V, Maraist M, Arfors K, Schatz D, Peck A, Cornelius J. Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic cells. Nature Medicine 6, 278-282. 2000.

9. Grapin-Botton A, Melton DA. Endoderm development: from patterning to organogenesis. Trends Genet 16[3], 124-130. 2000.

10. Peers B, Leonard J, Sharma S, Teitelman G, Montminy MR. Insulin expression in pancreatic islet cells relies on cooperative interactions between the helix loop helix factor E47 and the homeobox factor STF-1. Mol Endocrinol 1994; 8:1798-1806.

11. Peers B, Sharma S, Johnson T, Kamps M, Monteminy M. The pancreatic islet factor STF-1 binds cooperatively with Pbx to a regulatory element in the somatostatin promoter: importance of the FPWMK motif and of the homeodomain. Mol Cell Biol 1995; 15:7091-7097.

12. Serup P, Petersen HV, Pedersen EE, Edlund H, Leonard J, Petersen JS et al. The homeodomain protein IPF-1/STF-1 is expressed in a subset of islet cells and promotes rat

insulin 1 gene expression dependent on an intact E1 helix-loop-helix factor binding site. Biochem J 1995; 310:997-1003.

13. Ahlgren U, Jonsson J, Jonsson L, Simu K, Edlund H. beta-cell-specific inactivation of the mouse Ipf1/Pdx1 gene results in loss of the beta-cell phenotype and maturity onset diabetes. Genes Dev 1998; 12(12. :1763-1768.

14. Guz Y, Montminy MR, Stein R, Leonard J, Gamer LW, Wright CV et al. Expression of murine STF-1, a putative insulin gene transcription factor, in beta cells of pancreas, duodenal epithelium and pancreatic exocrine and endocrine progenitors during ontogeny. Development 1995; 121:11-18.

15. Wang H, Maechler P, Ritz-Laser B, Hagenfeldt K, Ishihara H, Philippe J et al. Pdx1 Level Defines Pancreatic Gene Expression Pattern and Cell Lineage Differentiation. J Biol Chem 276[27], 25279-25286. 7-6-2001.

16. Offield MF, Jetton TL, Labosky PA, Ray M, Stein RW, Magnuson MA et al. PDX-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum. Development 122[3], 983-995. 1996.

17. Stoffers HEJH, Kester ADM, Kaiser V, Rinkens PELM, Knottnerus JA. Diagnostic value of signs and symptoms associated with peripheral arterial occlusive disease seen in general practice: a multivariable approach. Med Decis Making 1997; 17(1. :61-70.

18. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 15[1], 106-110. 1997.

19. Edlund H. Transcribing pancreas. Diabetes 47[12], 1817-1823. 1998.

20. Jamal A, Lipsett M, Hazrati A, Maysinger D, Pittenger G, Taylor-Fishwick DA et al. INGAP Peptide Induces In Vitro Islet Cell Neogenesis from Human Duct-like Islet Progenitor Cells. Endocrine Society 2002.

21. Sharma A, Zangen DH, Reitz P. The homeodomain protein IDX-1 increases after an early burst of proliferation during pancreatic regeneration. Diabetes 48, 507-513. 1999.

22. Song SY, Gannon M, Washington MK. Expansion of Pdx-1-expressing pancreatic epithelium and islet neogenesis in transgenic mice overexpressing transforming growth factor alpha. Gastroenterology 117, 1416-1426. 1999.

23. Kritzik MR, Jones E, Chen Z. PDX-1 and Msx-2 expression in the regeneration and developing pancreas. J Endocrinol 163, 523-530. 1999.

24. Pittenger G, Malik R, Burcus N, Boulton AJ, Vinik A. Specific fiber deficits in sensorimotor diabetic polyneuropathy correspond to cytotoxicity against neuroblastoma cells of sera from

patients with diabetes. Diabetes Care 22[11]. 1999.

25. McCarthy BG, Hsieh ST, Stocks A, Hauer P, Macko C, Cornblath DR et al. Cutaneous innervation in sensory neuropathies: evaluation by skin biopsy. Neurology 1995; 45:1848-1855.

26. McArthur JC, Stocks EA, Hauer P, Cornblath DR, Griffin JW. Epidermal nerve fiber density: normative reference range and diagnostic efficiency. Arch Neurol 1998; 55(12. :1513-1520.

27. Basta B, Pittenger G, Ray M, Stansberry K, Vinik A. Intra-Epidermal Nerve Fiber Density (IENF. a New Marker for Small Fiber Neuropathy (SFNP. in Diabetes. Diabetes 51[Supplement 2]. 2002.

28. Thompson NW, Pasieka J, Fukuuchi A. Duodenal gastrinomas, duodenotomy, and duodenal exploration in the surgical management of Zollinger-Ellison syndrome. World J Surg 1993; 17(4. :455-462.

29. Pittenger G, Taylor-Fishwick DA, Kosuri S, Burcus N, Briscoe R, Rosenberg L et al. INGAP Peptide – An Initiator of Neuroendocrine Cell (PGP9.5. Development and Islet Transdifferentiation/Transcription Factor (PDX-1. Expression in Normal Dog Pancreas. Endocrine Society 2002.

30. Shih D, Heimesaat M, Kuwajima S, Stein R, Wright C, Stoffel M. Profound defects in pancreatic B-cell function in mice with combined heterozygous mutations in Pdx-1, Hnf-1a, and Hnf-3b. PNAS 99[6], 3818-3823. 3-19-2002.

31. Lee V, Stoffel M. Bone marrow: An extra-pancreatic hideout for the elusive pancreatic stem cell? J Clin Invest 111, 799-801. 2003.

32. Ben-Shushan E, Marshak S, Shoshkes M, Cerasi E, Melloul D. A pancreatic beta-cell-specific enhancer in the human PDX-1 gene is regulated by hepatocyte nuclear factor 3 beta (HNF-3beta. , HNF-1alpha, and SPs transcription factors. J Biol Chem 276[20], 17533-17540. 2001.

33. Edlund H. Developmental biology of the pancreas. Diabetes 50, S5-S9. 2001.

34. Sander M, German MS. The B cell transcription factors and the development of the pancreas. J Mol Med 75, 327-340. 1997.

35. St-Ogne L, Wehr R, Gruss P. Pancreas development and diabetes. Curr Opin Genet 9, 295-300. 1999.

36. Kim SK, Hebrok M. Intercullular signals regulating pancreas development and function. Genes Dev 15, 111-127. 2001.

37. Deutsch G, Jung J, Zheng M, Lora J, Zaret KS. A bipotential precursor population forpancreas and liver with in teh embryonic endoderm. Development 128, 871-881. 2001.

38. Ahlgren U, Pfaff SL, Jessell TM, Edlund T, Edlund H. Independent requirement for ISL1 in formation of pancreatic mesenchyme and islet cells. Nature 385[6613], 257-260. 1997.

39. Pictet RL, Rutter WJ. Development of the embryonic endocrine pancreas. In: Steiner DF, Freinkel N, editors. Handbook of Physiology, Section 7: endocrinology, vol. 1. Washington,D.C: American Physiological Society, 1972: 25-66.

40. Smith SB, Gasa R, Watada H, Wang J, Griffen SC, German MS. Neurogenin3 and hepatic nuclear factor 1 cooperate in activating pancreatic expression of Pax4. J Biol Chem 2003; 278(40. :38254-38259.

41. Rooman I, Heremans Y, Heimberg H, Bouwens L. Modulation of rat pancreatic acinoductal transdifferentiation and expression of PDX-1 in vitro. Diabetologia 43, 907-914. 2000.

42. Vinik A, Rafaeloff R, Pittenger G, Rosenberg L, Duguid W. Induction of pancreatic islet neogenesis. Horm Metab Res 1997; 29(6. :278-293.

43. Shih DQ, Screenan S, Munoz KN, Philipson L, Pontoglio M, Yaniv M et al. Loss of HNF-1alpha function in mice leads to abnormal expression of genes involved in pancreatic islet development and metabolism. Diabetes 50[11], 2472-2480. 2001.

44. Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, McKay R. Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets. Science 292[5520], 1389-1394. 2001.

45. Assady S, Maor GAM, Itskovitz-Eldor J, Skorecki K, Tzukerman M. Insulin Production by Human Embryonic Stem Cells. Diabetes 50, 1691-1697. 2001.

46. Soria B. Insulin-secreting cells deerived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. Diabetes 49, 157-162. 2000.

47. Beattie GM, Itkin-Ansari P, Cirulli V, Leibowitz G, Lopez AD, Bossie S et al. Sustained proliferatin of PDX-1+ cells derived from human islets. Diabetes 48[5], 1013-1019. 1999.

48. Cheung AT. Glucose-dependent insulin release from genetically engineered K cells. Science 290, 1959-1960. 2000.

49. Bonner-Weir S, Taneja M. In vitro cultivation of human islets from expanded ductal tissue. PNAS 97, 7999-8004. 7-5-2000.

50. Itkin-Ansari P, Demeterco C, Bossie S, de la Tour DD, Beattie GM, Movassat J et al. PDX-1 and cell-cell contact act in synergy to promote delta-cell development in a human pancreatic endocrine precursor cell line. Mol Endocrinol 14[6], 814-822. 2000.

51. Dufayet de La Tour D, Halvorsen T, Demeterco C, Tyrberg B, Itkin-Ansari P, Loy M et al. B-Cell Differentiation from a Human Pancreatic Cell Line in Vitro and in Vivo. Molecular

Endocrinology 15, 476-483. 2001.

52. Vinik A, Pittenger G, Rafaeloff R, Rosenberg L. Factors controlling pancreatic islet neogenesis. Tumour Biol 1993; 14:184-200.

53. Bertelli E, Regoli M, Orazioli D, Bendayan M. Association between islets of Langerhans and pancreatic ductal system in adult rat. Where endocrine and exocrine meet together? Diabetologia 44, 575-584. 2001.

54. Fiddian-Green RG, Pittenger G, Kothary P, Vinik AI. Role of calcium in the stimulus-secretion coupling of antral gastrin release. Endocrinology 1983; 112:753-760.

55. Bendayan M. Anatomic basis oc islet-acinar interaction in the pancreas. Regulatory Peptide Letter 1990; 2:8.

56. Creutzfeldt W, Folsch UR, Stockmann F. Clinical implications of islet-acinar interactions. Regulatory Peptide Letter 1990; 2:8.

57. Colon JM, Rouiller D, Boden G, Unger RH. Charactreization of immunoreactive components of inulin and somatostatin in canine pancreatic juice. FEBS Lett 105, 23-26. 1979.

58. Ertan A, Taminato T, Akdamar K. Immunoreactive somatostatin in human pancreatic secretion. J Clin Endocrinol Metab 52, 589-591. 1981.

59. Sarfati P, Green GM, Brazeau P, Morisset J. Presence of somatostatin-like immunoreactivity in rat pancreatic juice: a physilogical phenomenon. Can J Physiol Pharmacol 64, 539-544. 1986.

60. Buts JPDKN, Marandi S. Expression of insulin receptors and of 60-kDa receptor substrate in rat mature and immature enterocytes. Am J Physiol 273, G217-G226. 1997.

61. Gingerich RL, Gilbert WR, Comens PG, Gavin JR. Identification and characterization of insulin receptors in basolateral membranes of dog intestinal mucosa. Diabetes 36, 1124-1129. 1987.

62. Pillion DJ, Ganapathy V, Leibach FH. Identification of insulin receptors on the mucosal surface colon epithelial cells. J Biol Chem 260, 5244-5247. 1985.

63. Miyaura C, Chen L, Appel M, Alam T, Inman L, Hughes SD et al. Expression of reg/PSP, a pancreatic exocrine gene: relationship to changes in islet beta-cell mass. Mol Endocrinol 1991; 5:226-234.

64. Ohno T, Ishii C, Kato N. Increased expression of regenerating (reg. gene protein in neonatal rat pancreas treated with streptozotocin. Endocr J 42, 649-653. 1995.

65. Rafaeloff R, Barlow SW, Rosenberg L, Vinik AI. Expression of Reg gene in the Syrian

golden hamster pancreatic islet regeneration model. Diabetologia 1995; 38:906-913.

66. Zenilman ME, Chen J, Danesh B, Zhen QH. Characteristics of rat pancreatic regenerating protein. Surgery 124, 855-863. 1998.

67. Sanchez D, Baeza N, Blouin R, Devaux C, Grondin G, Mabrouk K et al. Overexpression of the reg Gene In Non-obese Diabetic Mouse Pancreas During Active Diabetogenesis Is Restricted to Exocrine Tissue. The Journal of Histochemistry and Cytochemistry 48[10], 1401-1410. 2000.

68. Anastasi E, Ponte E, Gradini R, Bulotta A, Sale P, Tiberti C et al. Expression of Reg and cytokeration 20 during ductal cell differentiation and proliferation in a mouse model of autoimmune diabetes. European Journal of Endocrinology 141, 644-652. 1999.

69. Abe M, Nata K, Akiyama T, Shervani NJ, Kobayashi S, Tomioka-Kumagai T et al. Identification of a novel Reg family gene, Reg IIIdelta, and mapping of all three types of Reg family gene in a 75 kilobase mouse genomic region. Gene 2000; 246(1-2. :111-122.

70. Rafaeloff R, Pittenger GL, Barlow SW, Qin XF, Yan B, Rosenberg L et al. Cloning and sequencing of the pancreatic islet neogenesis associated protein (INGAP. gene and its expression in islet neogenesis in hamsters. J Clin Invest 1997; 99(9. :2100-2109.

71. Sasahara K, Yamaoka T, Moritani M, Yoshimoto K, Kuroda Y, Itakura M. Molecular cloning and tissue-specific expression of a new member of the regenerating protein family, islet neogenesis-associated protein-related protein. Biochimica et Biophysica Acta 1500, 142-146. 2000.

72. Rosenberg L, Vinik AI. Regulation of pancreatic islet growth and differentiation – Evidence for paracrine and/or autocrine growth factor(s. . Clin Res 1990; 38:271A.

73. Brockenbrough JS, Weir GC, Bonner-Weir S. Discordance of exocrine and endocrine growth after 90% pancreatectomy in rats. Diabetes 1988; 37:232-236.

74. Pour P, Mohr U, Cardesa A, Althoff J, Kruger FW. Pancreatic neoplasms in an animal model: morphological, biological, and comparative studies. Cancer 1975; 36:379-389.

75. Rosenberg L, Duguid W, Vinik A. Induction of neuroblastosis will reverse diabetes in the Syrian golden hamster. Diabetes 37, 334. 1998.

76. Rosenberg L, Duguid WP, Vinik AI. Cell proliferation in the pancreas of the Syrian golden hamster. Dig Dis Sci 1987; 32:1185.

77. Sarvetnick N. Islet cell destruction and regeneration in IFN-gamma transgenic mice. J.Cell Biochem. CB019, 49. 1991.

78. Smith D, Scarffe J, Wagstaff J, Johnston R. Phase II trial of rDNA alfa 2b interferon in

patients with malignant carcinoid tumor. Cancer Treat Rep 71, 1265. 1987.

79. Takasawa S, Yamamoto H, Terazono K, Okamoto H. Novel gene activated in rat insulinomas. Diabetes 1986; 35:1178-1180.

80. Terazono K, Uchiyama Y, Ide M, Watanabe T, Yonekura H, Yamamoto H et al. Expression of reg protein in rat regenerating islets and its co- localization with insulin in the beta cell secretory granules. Diabetologia 1990; 33:250-252.

81. Terazono K, Yamamoto H, Takasawa S. A novel gene activated in regeneratin islets. J Biol Chem 262, 2111. 1990.

82. Watanabe T, Yonekura H, Terazono K, Yamamoto H, Okamoto H. Complete nucleotide sequence of human reg gene and its expression in normal and tumoral tissues. The reg protein, pancreatic stone protein, and pancreatic thread protein are one and the same product of the gene. J Biol Chem 1990; 265:7432-7439.

83. Vinik A, Pittenger G, Pavlic-Renar I. Role of growth factors in pancreatic endocrine cells. Endocrinol Metab Clin North Am 22, 875. 1993.

84. Ahlman H, Wangberg B, Nilsson O. Growth regulation in carcinoid tumors. Endocrinol Metab Clin North Am 22, 889. 1993.

85. Chaudhry A, Funa K, Oberg K. Expression of growth peptides and their receptors in neuroendocrine tumors of the digestive system. Acta Oncol 32, 107. 1993.

86. Kerr JFR, Wyllie AH, Currie AR. Br J Cancer 1972; 26:239-257.

87. Perry R, Kang Y, Greaves B. Effects of tamoxifen on growth and apoptosis of estrogen-dependent and independent human breat cancer cells. Ann Surg Oncol 2, 238-245. 1995.

88. Rotello R, Lieberman R, Purchio A, Gerscgebson L. Coordinated regulation of apoptosis and cell proliferation by transforming growth factor. Proc Natl Acad Sci 88, 3412. 1991.

89. Szende B, Zalatnia A, Schaly AV. Programmed cell death (apoptosis. in pancreatic cancers of hamsters after treatment with analogs of both luteinizing hormone-releasing hormone and somatostatin. Proc Natl Acad Sci 86, 1643. 1989.

90. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature 321, 85. 1988.

91. Thakker R, Bouloux P, Wooding C. Association of parathyroid tumors in multiple endocrine neoplasia type 1 with loss of alleles on chromosome 11. N Engl J Med 332[218]. 1989.

92. Brandi ML, Aurbach GD, Fitzpatrick LA, Quarto R, Spiegel AM, Bliziotes MM et al. Parathyroid mitogenic activity in plasma from patients with familial multiple endocrine neoplasia

type 1. N Engl J Med 1986; 314(20. :1287-1293.

93. Marx SJ, Vinik AI, Santen RJ, Floyd JC, Jr., Mills JL, Green J. Multiple endocrine neoplasia type I: assessment of laboratory tests to screen for the gene in a large kindred. Medicine (Baltimore. 1986; 65:226-241.

94. Owerbach D, Bell GI, Rutter WJ, Brown JA, Shows TB. The insulin gene is located on the short arm of chromosome 11 in humans. Diabetes 1981; 30(3. :267-270.

95. Eisenbarth GS, Shimizu K, Bowring MA, Wells S. Expression of receptors for tetanus toxin and monoclonal antibody A2B5 by pancreatic islet cells. Proc Natl Acad Sci U S A 1982; 79:5066-5070.

96. McLeod MK, Fukuuchi A, Warnock M, Tuteta A, Vinik A. Mechanisms of stimulatory and inhibitory effects of somatostatin on cell proliferation in rat insulinoma (RIN m5F. cell line. Abstract . 1991.

97. Larsson C, Weber G, Teh BT, Lagercrantz J. Genetics of multiple endocrine neoplasia type 1. Ann N Y Acad Sci 1994; 733:453-463.

98. Mozell EJ, Cramer AJ, O'Dorisio TM, Woltering EA. Long-term efficacy of octreotide in the treatment of Zollinger-Ellison syndrome. Arch Surg 1992; 127(9. :1019-1024.

99. Donis-Keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet 1993; 2(7. :851-856.

100. Carlson KM, Dou S, Chi D, Scavarda N, Toshima K, Jackson CE et al. Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. Proc Natl Acad Sci U S A 1994; 91(4. :1579-1583.

101. Hofstra RM, Landsvater RM, Ceccherini I, Stulp RP, Stelwagen T, Luo Y et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 1994; 367(6461. :375-376.

102. Bissette G, Manberg P, Nemeroff CB, Prange AJ, Jr. Neurotensin, a biologically active peptide. Life Sci 1978; 23(22. :2173-2182.

103. Blackburn AM, Bryant MG, Adrian TE, Bloom SR. Pancreatic tumours produce neurotensin. J Clin Endocrinol Metab 1981; 52(4. :820-822.

104. Sundler F, Alumets J, Hakanson R. Peptides in the gut with dual distribution in nerves and endocrine cells. SR Bloom, editor. In Gut Hormones , 406. 1978. Churchill Livingston.

105. Wynick D, Williams SJ, Bloom SR. Symptomatic secondary hormone syndromes in patients with established malignant pancreatic endocrine tumors. N Engl J Med 1988; 319(10.

:605-607.

106. Lloyd RV. Practical markers used in the diagnosis of neuroendocrine tumors. Endocr Pathol 2003; 14(4. :293-301.

107. Lloyd RV. Practical markers used in the diagnosis of neuroendocrine tumors. Endocr Pathol 2003; 14(4. :293-301.

108. Martinez A, Montuenga LM, Springall DR, Treston A, Cuttitta F, Polak JM. Immunocytochemical localization of peptidylglycine alpha-amidating monooxygenase enzymes (PAM. in human endocrine pancreas. J Histochem Cytochem 1993; 41(3. :375-380.

109. Curry WJ, Barkatullah SC, Johansson AN, Quinn JG, Norlen P, Connolly CK et al. WE-14, a chromogranin a-derived neuropeptide. Ann N Y Acad Sci 2002; 971:311-316.

110. Steel JH, Bishop AE. Molecular approaches to neuroendocrine pathology. Cancer Metastasis Rev 1997; 16(1-2. :179-205.

111. Scopsi L, Sampietro G, Boracchi P, Collini P. Argyrophilia and chromogranin A and B immunostaining in patients with sporadic medullary thyroid carcinoma. A critical appraisal of their prognostic utility. J Pathol 1998; 184(4. :414-419.

112. DeLellis RA. Proliferation markers in neuroendocrine tumors: useful or useless? A critical reappraisal. Verh Dtsch Ges Pathol 1997; 81:53-61.

113. DeLellis RA. The neuroendocrine system and its tumors: an overview. Am J Clin Pathol 2001; 115 Suppl:S5-16.

114. Reubi JC. Use of receptor autoradiography for the visualization of somatostatin receptors in human pituitary adenomas and other neuroendocrine tumors. J Endocrinol Invest 12, 18. 1989.

115. Buchanan KD, Johnston CF, O'Hare MM, Ardill JE, Shaw C, Collins JS et al. Neuroendocrine tumors. A European view. Am J Med 1986; 81(6B. :14-22.

116. BIORCK G, AXEN O, THORSON A. Unusual cyanosis in a boy with congenital pulmonary stenosis and tricuspid insufficiency. Fatal outcome after angiocardiography. Am Heart J 1952; 44(1. :143-148.

117. Davis Z, Moertel CG, McIlrath DC. The malignant carcinoid syndrome. Surg Gynecol Obstet 1973; 137(4. :637-644.

118. Solcia E, Capella C, Buffa R. Morphological and functional classification of endocrine cells and related growths in the gastrointestinal tract. GBJ Glass, editor. Gastrointestinal Hormones , 1. 1980.

119. Weil C. Gastroenteropancreatic endocrine tumors. Klin Wochenschr 1985; 63(10. :433-459.

120. Carney JA, Go VL, Fairbanks VF, Moore SB, Alport EC, Nora FE. The syndrome of gastric argyrophil carcinoid tumors and nonantral gastric atrophy. Ann Intern Med 1983; 99(6. :761-766.

121. Eckhauser FE, Lloyd RV, Thompson NW, Raper SE, Vinik AI. Antrectomy for multicentric, argyrophil gastric carcinoids: a preliminary report. Surgery 1988; 104(6. :1046-1053.

122. Cameron SJ, Doig A. Cerebellar tumours presenting with clinical features of phaeochromocytoma. Lancet 1970; 1(7645. :492-494.

123. Wiedenmann B, Franke WW, Kuhn C, Moll R, Gould VE. Synaptophysin: a marker protein for neuroendocrine cells and neoplasms. Proc Natl Acad Sci U S A 1986; 83:3500-3504.

124. Simpson S, Vinik AI, Marangos PJ, Lloyd RV. Immunohistochemical localization of neuron-specific enolase in gastroenteropancreatic neuroendocrine tumors. Correlation with tissue and serum levels of neuron-specific enolase. Cancer 1984; 54(7. :1364-1369.

125. Kolby L, Bernhardt P, Sward C, Johanson V, Ahlman H, Forssell-Aronsson E et al. Chromogranin A as a determinant of midgut carcinoid tumour volume. Regul Pept 2004; 120(1-3. :269-273.

126. Nehar D, Lombard-Bohas C, Olivieri S, Claustrat B, Chayvialle JA, Penes MC et al. Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxf. 2004; 60(5. :644-652.

127. De Block CE, Colpin G, Thielemans K, Coopmans W, Bogers JJ, Pelckmans PA et al. Neuroendocrine tumor markers and enterochromaffin-like cell hyper/dysplasia in type 1 diabetes. Diabetes Care 2004; 27(6. :1387-1393.

128. Gould M, Johnson RJ. Computed tomography of abdominal carcinoid tumour. Br J Radiol 1986; 59(705. :881-885.

129. Kressel HY. Strategies for magnetic resonance imaging of focal liver disease. Radiol Clin North Am 1988; 26(3. :607-615.

130. Eriksson B, Bergstrom M, Lilja A, Ahlstrom H, Langstrom B, Oberg K. Positron emission tomography (PET. in neuroendocrine gastrointestinal tumors. Acta Oncol 1993; 32(2. :189-196.

131. Eriksson B, Lilja A, Ahlstrom H, Bjurling P, Bergstrom M, Lindner KJ et al. Positron-emission tomography as a radiological technique in neuroendocrine gastrointestinal tumors. Ann N Y Acad Sci 1994; 733:446-452.

132. Sisson JC, Shapiro B, Beierwaltes WH. Treatment of malignant pheochromocytoma with a new radiopharmaceutical. Trans Assoc Am Physicans 96, 209. 1983.

133. Fischer M, Kamanabroo D, Sonderkamp H, Proske T. Scintigraphic imaging of carcinoid tumours with 131I-metaiodobenzylguanidine. Lancet 1984; 2(8395. :165.

134. Shapiro B. MIBG in the diagnosis and therapy of neuroblastoma and pheo-chromocytoma. In the Proceedings of the International Symposium on Recent Advances in Nuclear Medicine. E Cattaruiz, E Englaro, O Geatti, editors. Surin Biomedica , 129. 1987.

135. Shapiro B. MIBG in the management of neuroendocrine tumors. Presented at the International Congress on Advances in Management of Malignances , 129. 1988.

136. Sinzinger H, Renner F, Granegger S. Unsuccessful iodine-131 MIBG imaging of carcinoid tumors and apudomas. J Nucl Med 1986; 27(7. :1221-1222.

137. Von Moll L, McEwan AJ, Shapiro B, Sisson JC, Gross MD, Lloyd R et al. Iodine-131 MIBG scintigraphy of neuroendocrine tumors other than pheochromocytoma and neuroblastoma. J Nucl Med 1987; 28(6. :979-988.

138. Marx SJ, Vinik AI, Santen RJ, Floyd JC, Jr., Mills JL, Green J, III. Multiple endocrine neoplasia type I: assessment of laboratory tests to screen for the gene in a large kindred. Medicine (Baltimore. 1986; 65(4. :226-241.

139. Shapiro B, Sisson JC. Sympatho-adrenal imaging with radioiodinated metaiodobenzylguanidine. Lippincott, editor. In Atlas of Nuclear Medicine , 72. 1988. D Von Nostrand, S Baum.

140. Geatti O, Shapiro B, Sisson JC, Hutchinson RJ, Mallette S, Eyre P et al. Iodine-131 metaiodobenzylguanidine scintigraphy for the location of neuroblastoma: preliminary experience in ten cases. J Nucl Med 1985; 26(7. :736-742.

141. Lumbroso J, Guermazi F, Hartmann O, Coornaert S, Rabarison Y, Lemerle J et al. [Sensitivity and specificity of meta-iodobenzylguanidine (mIBG. scintigraphy in the evaluation of neuroblastoma: analysis of 115 cases]. Bull Cancer 1988; 75(1. :97-106.

142. Treuner J, Feine U, Niethammer D, Muller-Schaumburg W, Meinke J, Eibach E et al. Scintigraphic imaging of neuroblastoma with [131-I]iodobenzylguanidine. Lancet 1984; 1(8372. :333-334.

143. Kubota A, Yamada Y, Kagimoto S. Identification of somatostatin receptor subtypes and an implication for the efficacy of somatostatin analogue SMS 201-995 in treatment of human endocrine tumors. J Clin Invest 93, 1321. 1994.

144. O'Steen WK, Barnard JL, Jr., Yates RD. Morphologic changes in skeletal muscle induced by serotonin treatment: a light- and electron-microscope study. Exp Mol Pathol 1967; 7(2. :145-155.

145. Frolich JC, Bloomgarden ZT, Oates JA, McGuigan JE, Rabinowitz D. The carcinoid flush.

Provocation by pentagastrin and inhibition by somatostatin. N Engl J Med 1978; 299(19. :1055-1057.

146. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993; 20(8. :716-731.

147. Krenning EP, Kwekkeboom DJ, Oei HY, de Jong RJ, Dop FJ, Reubi JC et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann N Y Acad Sci 1994; 733:416-424.

148. Virgolini I, Patri P, Novotny C, Traub T, Leimer M, Fuger B et al. Comparative somatostatin receptor scintigraphy using in-111-DOTA-lanreotide and in-111-DOTA-Tyr3-octreotide versus F-18-FDG-PET for evaluation of somatostatin receptor-mediated radionuclide therapy. Ann Oncol 2001; 12 Suppl 2:S41-S45.

149. Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC. Somatostatin receptor scintigraphy. L M Freeman, editor. In Nuclear Medicine Annual , 1-50. 1995. Raven Press.

150. Lebtahi R, Cadiot G, Sarda L, Daou D, Faraggi M, Petegnief Y et al. Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. J Nucl Med 1997; 38(6. :853-858.

151. Lebtahi R, Cadiot G, Mignon M, Le Guludec D. Somatostatin receptor scintigraphy: a first-line imaging modality for gastroenteropancreatic neuroendocrine tumors. Gastroenterology 1998; 115(4. :1025-1027.

152. Gibril F, Reynolds JC, Doppman JL, Chen CC, Venzon DJ, Termanini B et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. Ann Intern Med 1996; 125(1. :26-34.

153. Termanini B, Gibril F, Reynolds JC, Doppman JL, Chen CC, Stewart CA et al. Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. Gastroenterology 1997; 112(2. :335-347.

154. Gibril F, Reynolds JC, Chen CC, Yu F, Goebel SU, Serrano J et al. Specificity of somatostatin receptor scintigraphy: a prospective study and effects of false-positive localizations on management in patients with gastrinomas. J Nucl Med 1999; 40(4. :539-553.

155. Janson ET, Westlin JE, Eriksson B, Ahlstrom H, Nilsson S, Oberg K. [111In-DTPA-D-Phe1]octreotide scintigraphy in patients with carcinoid tumours: the predictive value for somatostatin analogue treatment. Eur J Endocrinol 1994; 131(6. :577-581.

156. Kvols LK, Reubi JC, Horisberger U, Moertel CG, Rubin J, Charboneau JW. The presence of somatostatin receptors in malignant neuroendocrine tumor tissue predicts responsiveness to octreotide. Yale J Biol Med 1992; 65(5. :505-518.

157. Strodel WE, Vinik AI, Jaffe BM, Eckhauser FE, Thompson NW. Substance P in the localization of a carcinoid tumor. J Surg Oncol 1984; 27(2. :106-111.

158. Feldman JM. Urinary serotonin in the diagnosis of carcinoid tumors. Clin Chem 1986; 32(5. :840-844.

159. Melmon KL, Sjoerdsma A, Oates JA, LASTER L. TREATMENT OF MALABSORPTION AND DIARRHEA OF THE CARCINOID SYNDROME WITH METHYSERGIDE. Gastroenterology 1965; 48:18-24.

160. Sandler M, Karim SM, Williams ED. Prostaglandins in amine-peptide-secreting tumours. Lancet 1968; 2(7577. :1053-1054.

161. Alumets J, Hakanson R, Ingemansson S, Sundler F. Substance P and 5-HT in granules isolated from an intestinal argentaffin carcinoid. Histochemistry 1977; 52(3. :217-222.

162. Oates JA, Pettinger WA, Doctor RB. Evidence for the release of bradykinin in carcinoid syndrome. J Clin Invest 1966; 45(2. :173-178.

163. PERNOW B, WALDENSTROM J. Determination of 5-hydroxytryptamine, 5-hydroxyindole acetic acid and histamine in thirty-three cases of carcinoid tumor (argentaffinoma. . Am J Med 1957; 23(1. :16-25.

164. Wilander E, Grimelius L, Portela-Gomes G, Lundqvist G, Skoog V, Westermark P. Substance P and enteroglucagon-like immunoreactivity in argentaffin and argyrophil midgut carcinoid tumours. Scand J Gastroenterol Suppl 1979; 53:19-25.

165. Lucas KJ, Feldman JM. Flushing in the carcinoid syndrome and plasma kallikrein. Cancer 1986; 58(10. :2290-2293.

166. Feldman JM. Increased dopamine production in patients with carcinoid tumors. Metabolism 1985; 34(3. :255-260.

167. Theodorsson-Norheim E, Norheim I, Oberg K, Brodin E, Lundberg JM, Tatemoto K et al. Neuropeptide K: a major tachykinin in plasma and tumor tissues from carcinoid patients. Biochem Biophys Res Commun 1985; 131(1. :77-83.

168. Vinik A, Strodel WE, O'Dorisio TM. Endocrine tumors of the gastroenteropancreatic axis. R J Stanten, A Manni, editors. In Diagnosis and Management of Endocrine-Related Tumors , 305. 1984. Martinus Nijhoff.

169. Feldman JM, O'Dorisio TM. Role of neuropeptides and serotonin in the diagnosis of carcinoid tumors. Am J Med 1986; 81(6B. :41-48.

170. Vinik A, Achem-Karam S, Owyang C. Gastrointestinal hormones in clinical medicine. MP Cohen, PP Foa, editors. In Special Topics in Endocrinology and Metabolism , 93-138. 1982.

New York: Alan R. Liss.

171. UDENFRIEND S, TITUS E, WEISSBACH H. The identification of 5-hydroxy-3-indoleacetic acid in normal urine and a method for its assay. J Biol Chem 1955; 216(2. :499-505.

172. Das ML. A rapid, sensitive method for direct estimation of serotonin in whole blood. Biochem Med 1972; 6(4. :299-309.

173. Davis RB. The concentration of serotonin in normal human serum as determined by an improved method. J Lab Clin Med 24, 177. 1973.

174. Walker TP. The determination of serotonin (5-hydroxtryptamine. in human blood. J Lab Clin Med 55, 824. 1959.

175. Modlin IM. Carcinoid syndrome. J Clin Gastroenterol 1980; 2(4. :349-354.

176. Aldrich LB, Moattari AR, Vinik AI. Distinguishing features of idiopathic flushing and carcinoid syndrome. Arch Intern Med 1988; 148(12. :2614-2618.

177. Ahlman H, Dahlstrom A, Gronstad K, Tisell LE, Oberg K, Zinner MJ et al. The pentagastrin test in the diagnosis of the carcinoid syndrome. Blockade of gastrointestinal symptoms by ketanserin. Ann Surg 1985; 201(1. :81-86.

178. Kaplan EL, Jaffe BM, Peskin GW. A new provocative test for the diagnosis of the carcinoid syndrome. Am J Surg 1972; 123(2. :173-179.

179. Conlon JM, Deacon CF, Richter G, Stockmann F, Creutzfeldt W. Circulating tachykinins (substance P, neurokinin A, neuropeptide K. and the carcinoid flush. Scand J Gastroenterol 1987; 22(1. :97-105.

180. Norheim I, Theodorsson-Norheim E, Brodin E, Oberg K. Tachykinins in carcinoid tumors: their use as a tumor marker and possible role in the carcinoid flush. J Clin Endocrinol Metab 1986; 63(3. :605-612.

181. Hoefnagel CA, Marcuse HR, DeKraker J, Voute PA. Detection of neuroblastoma with I-131-meta-iodobenzylguanidine. Clin Biol Res 137, 142. 1979.

182. Roberts WC. A unique heart disease associated with a unique cancer: Carcinoid heart disease. Amer J Cardiol 80, 251-256. 1997.

183. Anderson AS, Krauss D, Lang R. Cardiovascular complications of malignant carcinoid disease. Am Heart J 1997; 134(4. :693-702.

184. Callahan JA, Wroblewski EM, Reeder GS, Edwards WD, Seward JB, Tajik AJ. Echocardiographic features of carcinoid heart disease. Am J Cardiol 1982; 50(4. :762-768.

185. Lundin L, Landelius A, Oberg K. Transesophageal echocardiography improves the diagnostic value of cardiac ultrasound in patients with carcinoid heart disease. Br Heart J 64, 190-194. 1991.

186. Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. Circulation 1993; 87(4. :1188-1196.

187. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337(9. :581-588.

188. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvols LK. Outcome of cardiac surgery for carcinoid heart disease. J Am Coll Cardiol 1995; 25(2. :410-416.

189. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. Circulation 1988; 77(2. :264-269.

190. Ribiolio P, Wilson J, Harrison J, Sanders L, Bashore T, Feldman J. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 92, 790-795. 1998.

191. Vinik A, Perry R. Neoplasms of the Gastroenteropancreatic Endocrine System. Williams & Wilkins, editor. Cancer Medicine , 1605-1641. 1997. Baltimore.

192. Perry RR, Vinik AI. Endocrine tumors of the gastrointestinal tract. Annu Rev Med 1996; 47:57-68.

193. Lundin L, Oberg K, Landelius J, Hansson HE, Wilander E, Theodorsson E. Plasma atrial natriuretic peptide in carcinoid heart disease. Am J Cardiol 1989; 63(13. :969-972.

194. Ribiolio P, Rigolin V, Harrison J, Lowe J, Moore J, Bashore T et al. Predictors of outcome of tricuspid valve replacement in carcinoid heart disease. Am J Cardiol 75, 485-488. 1995.

195. Rayson D, Pitot H, Kvols L. Regression of carcinoid tumor after valvular surgery for carcinoid heart disease. Cancer 79[3], 605-611. 1997.

196. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. J Clin Oncol 1983; 1(11. :727-740.

197. Godwin JD. Carcinoid tumors. An analysis of 2,837 cases. Cancer 1975; 36(2. :560-569.

198. Kvols LK. Metastatic carcinoid tumors and the carcinoid syndrome. A selective review of chemotherapy and hormonal therapy. Am J Med 1986; 81(6B. :49-55.

199. Maton PN, Camilleri M, Griffin G, Allison DJ, Hodgson HJ, Chadwick VS. Role of hepatic arterial embolisation in the carcinoid syndrome. Br Med J (Clin Res Ed. 1983; 287(6397. :932-935.

200. Gyr NE, Kayasseh L, Keller U. Somatostatin as a therapeutic agent. Edinburgh: Churchhill Livingstone, editor. In Gut Hormones 2[Edited by SR Bloom, JM Polak], 581. 1981.

201. Sheppard M, Shapiro B, Pimstone B, Kronheim S, Berelowitz M, Gregory M. Metabolic clearance and plasma half-disappearance time of exogenous somatostatin in man. J Clin Endocrinol Metab 1979; 48(1. :50-53.

202. Strodel WE, Vinik A, Thompson NW, Eckhauser FE, Talpos GB. Small bowel carcinoid tuimors and the carcinoid syndrome. NW Thompson, Vinik A, editors. In Endocrine Surgery Update , 293. 1983. New York: Grune & Stratton.

203. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985; 313(19. :1229-1230.

204. Vinik AI, Tsai ST, Moattari AR, Cheung P, Eckhauser FE, Cho K. Somatostatin analogue (SMS 201-995. in the management of gastroenteropancreatic tumors and diarrhea syndromes. Am J Med 1986; 81(6B. :23-40.

205. 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(11. :663-666.

206. Richter G, Stockman F, Lembeke B, Conlon JM, Creutzfeldt W. Short-term administration of somatostatin analogue SMS-201-995 in patients with carcinoid tumors. Scand J Gastroenterol. 21, 193. 1986.

207. Santangelo WC, O'Dorisio TM, Kim JG, Severino G, Krejs GJ. Pancreatic cholera syndrome: effect of a synthetic somatostatin analog on intestinal water and ion transport. Ann Intern Med 1985; 103(3. :363-367.

208. Arnold R, Lankisch PG. Somatostatin and the gastrointestinal tract. Clin Gastroenterol 1980; 9(3. :733-753.

209. Stockmann F, Richter G, Lembeke B, Conlon JM, Creutzfeldt W. Long-term treatment of patients with endocrine gastrointestinal tumors with the somatostatin analogue SMS 201-995. Scand J Gastroenterol. 21, 230. 1986.

210. Hengl G, Prager J, Pointner H. The influence of somatostatin on the absorption of triglycerides in partially gastrectomized subjects. Acta Hepatogastroenterol (Stuttg. 1979; 26(5. :392-395.

211. Vinik A, Moattari AR. Use of somatostatin analog in management of carcinoid syndrome.

Dig Dis Sci 1989; 34(3 Suppl. :14S-27S.

212. Poole CJ. Myelopathy secondary to metastatic carcinoid tumour. J Neurol Neurosurg Psychiatry 1984; 47(12. :1359-1360.

213. Berry EM, Maunder C, Wilson M. Carcinoid myopathy and treatment with cyproheptadine (Periactin. . Gut 1974; 15(1. :34-38.

214. GREEN D, JOYNT RJ, VANALLEN MW. NEUROMYOPATHY ASSOCIATED WITH A MALIGNANT CARCINOID TUMOR. A CASE REPORT. Arch Intern Med 1964; 114:494-496.

215. Wroe SJ, Ardron M, Bowden AN. Myasthenia gravis associated with a hormone producing malignant carcinoid tumour. J Neurol Neurosurg Psychiatry 1985; 48(7. :719-720.

216. Kraenzlin ME, Ch'ng JL, 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 1985; 88(1 Pt 1. :185-187.

217. Saltz L, Trochanowski B, Buckley M, Heffernan B, Niedzwiecki D, Tao Y et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. Cancer 1993; 72(1. :244-248.

218. Anthony L, Johnson D, Hande K, Shaff M, Winn S, Krozely M et al. Somatostatin analogue phase I trials in neuroendocrine neoplasms. Acta Oncol 1993; 32(2. :217-223.

219. Janson ET, Oberg K. Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. Acta Oncol 1993; 32(2. :225-229.

220. Kvols LK. Therapy of the malignant carcinoid syndrome. Endocrinol Metab Clin North Am 1989; 18(2. :557-568.

221. McEwan AJ, Shapiro B, Sisson JC, Beierwaltes WH, Ackery DM. Radio-iodobenzylguanidine for the scintigraphic location and therapy of adrenergic tumors. Semin Nucl Med 1985; 15(2. :132-153.

222. Sisson JC, Shapiro B, Beierwaltes WH, Glowniak JV, Nakajo M, Mangner TJ et al. Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med 1984; 25(2. :197-206.

223. Sisson JC, Shapiro B, Beierwaltes WH. Treatment of malignant pheochromocytoma with a new radiopharmaceutical. J Nucl.Med 25, 197. 1984.

224. Sninsky CA, Wolfe MM, Martin JL, Howe BA, O'Dorisio TM, McGuigan JE et al. Myoelectric effects of vasoactive intestinal peptide on rabbit small intestine. Am J Physiol 1983; 244(1. :G46-G51.

225. Lamberts SW, Krenning EP, Klijn JG, Reubi JC. The clinical use of somatostatin analogues in the treatment of cancer. Baillieres Clin Endocrinol Metab 1990; 4(1. :29-49.

226. Schubert ML. In vivo somatostatin receptor imaging in the detection and treatment of gastrointestinal cancer. Gastroenterology 1991; 100(4. :1143-1144.

227. Carrasco CH, Charnsangavej C, Ajani J, Samaan NA, Richli W, Wallace S. The carcinoid syndrome: palliation by hepatic artery embolization. AJR Am J Roentgenol 1986; 147(1. :149-154.

228. Mekhjian HS, O'Dorisio TM. VIPoma syndrome. Semin Oncol 1987; 14(3. :282-291.

229. Melia WM, Nunnerley HB, Johnson PJ, Williams R. Use of arterial devascularization and cytotoxic drugs in 30 patients with the carcinoid syndrome. Br J Cancer 1982; 46(3. :331-339.

230. Nobin A, Mansson B, Lunderquist A. Evaluation of temporary liver dearterialization and embolization in patients with metastatic carcinoid tumour. Acta Oncol 1989; 28(3. :419-424.

231. Moertel CG. An odyssey in the land of small tumors. J Clin Oncol 5, 1502. 1989.

232. Moertel CG, Johnson CM, McKusick MA, Martin JK, Jr., Nagorney DM, Kvols LK et al. The management of patients with advanced carcinoid tumors and islet cell carcinomas. Ann Intern Med 1994; 120(4. :302-309.

233. van Hazel GA, Rubin J, Moertel CG. Treatment of metastatic carcinoid tumor with dactinomycin or dacarbazine. Cancer Treat Rep 1983; 67(6. :583-585.

234. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials 1979; 2(4. :327-334.

235. Kvols LK, Buck M. Chemotherapy of endocrine malignancies: a review. Semin Oncol 1987; 14(3. :343-353.

236. Kessinger A, Foley JF, Lemon HM. Therapy of malignant APUD cell tumors. Effectiveness of DTIC. Cancer 1983; 51(5. :790-794.

237. Bukowski RM, Tangen CM, Peterson RF, Taylor SA, Rinehart JJ, Eyre HJ et al. Phase II trial of dimethyltriazenoimidazole carboxamide in patients with metastatic carcinoid. A Southwest Oncology Group study. Cancer 1994; 73(5. :1505-1508.

238. Kelsen D, Fiore J, Heelan R, Cheng E, Magill G. Phase II trial of etoposide in APUD tumors. Cancer Treat Rep 1987; 71(3. :305-307.

239. Moertel CG, Rubin J, O'Connell MJ. Phase II study of cisplatin therapy in patients with metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Treat Rep 1986; 70(12. :1459-1460.

240. Mengel CE, Shaffer RD. The carcinoid syndrome. JF Holland, E Frei, editors. In Cancer Medicine . 1973. Philadelphia: Lea & Febiger.

241. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO, Jr. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol 1984; 2(11. :1255-1259.

242. Bukowski RM, Johnson KG, Peterson RF, Stephens RL, Rivkin SE, Neilan B et al. A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. A Southwest Oncology Group Study. Cancer 1987; 60(12. :2891-2895.

243. Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. Eur J Cancer Clin Oncol 1989; 25(10. :1475-1479.

244. Feldman JM. Carcinoid tumors and the carcinoid syndrome. Curr Probl Surg 1989; 26(12. :835-885.

245. Oberg K, Eriksson B. Medical treatment of neuroendocrine gut and pancreatic tumors. Acta Oncol 1989; 28(3. :425-431.

246. Hanssen LE, Schrumpf E, Kolbenstvedt AN, Tausjo J, Dolva LO. Treatment of malignant metastatic midgut carcinoid tumours with recombinant human alpha2b interferon with or without prior hepatic artery embolization. Scand J Gastroenterol 1989; 24(7. :787-795.

247. Sisson JC, Hutchinson RJ, Johnson J. Acute toxicity of therapeutic I-131-MIBG relates more to whole body than to blood radiation dosimetry. J Nucl Med 23, 618. 1987.

248. Oberg K. The action of interferon alpha on human carcinoid tumours. Semin Cancer Biol 3, 35. 1992.

249. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. J Clin Oncol 7, 865-868. 1989.

250. Ajani J, Carrasco C, Charnsangavej C. Islet cell tumors metastatic to the liver: effective palliation by seuential hepatic artery embolization. Proc Am Soc Clin Oncol 4, 80. 1989.

251. Moertel CG, May GR, Martin JK, Rubin J, Schutt AJ. Sequential hepatic artery occlusion (HAO. and chemotherapy for metastic carcinoid tumor and islet cell carcinoma (ICC. . Proc Am Soc Clin Oncol 4, 80. 1985.

252. Fajans S, Vinik A. Diagnosis and treatment of insulinoma. RJ Santen, A Manni, editors. In Diagnosis and Management of Endocrine-Related Tumors . 1984. Boston: Martinus Nijhoff.

253. Edis AJ, McIlrath DC, van Heerden JA, Fulton RE, Sheedy PF, Service FJ et al. Insulinoma–current diagnosis and surgical management. Curr Probl Surg 1976; 13(10. :1-45.

254. Friesen SR. Treatment of the Zollinger-Ellison syndrome. A 25 year assessment. Am J Surg 1982; 143(3. :331-338.

255. Thompson NW, Eckhauser FE. Malignant islet-cell tumors of the pancreas. World J Surg 1984; 8(6. :940-951.

256. Thompson NW. The surgical treatment of islet cell turmors of the pancreas. T L Dent, editor. In Pancreatic Disease , 461. 1981. New York: Grune & Stratton.

257. Glaser B, Shapiro B, Glowniak J, Fajans SS, Vinik AI. Effects of secretin on the normal and pathological beta-cell. J Clin Endocrinol Metab 1988; 66:1138-1143.

258. Vinik A, Strodel WE, Cho K, Eckhauser FE, Thompson N. Localization of hormonally active gastrointestinal tumors. NW Thompson, AI Vinik, editors. In Endocrine Surgery Update . 1983. New York: Grune & Stratton.

259. Glowniak JV, Shapiro B, Vinik AI, Glaser B, Thompson NW, Cho KJ. Percutaneous transhepatic venous sampling of gastrin: value in sporadic and familial islet-cell tumors and G-cell hyperfunction. N Engl J Med 1982; 307(5. :293-297.

260. Kaplan EL, Lee CH. Recent advances in the diagnosis and treatment of insulinomas. Surg Clin North Am 1979; 59(1. :119-129.

261. Le Quesne LP, Nabarro JD, Kurtz A, Zweig S. The management of insulin tumours of the pancreas. Br J Surg 1979; 66(6. :373-378.

262. Modlin IM. Endocrine tumors of the pancreas. Surg Gynecol Obstet 1979; 149(5. :751-769.

263. Stefanini P, Carboni M, Patrassi N, Basoli A. Beta-islet cell tumors of the pancreas: results of a study on 1,067 cases. Surgery 1974; 75(4. :597-609.

264. Robins JM, Bookstein JJ, Oberman HA, Fajans SS. Selective angiography in localizing islet-cell tumors of the pancreas. A further appraisal. Radiology 1973; 106(3. :525-528.

265. Doppman JL, Miller DL, Chang R, Shawker TH, Gorden P, Norton JA. Insulinomas: localization with selective intraarterial injection of calcium. Radiology 1991; 178(1. :237-241.

266. Cho KJ, Vinik AI, Thompson NW, Shields JJ, Porter DJ, Brady TM et al. Localization of the source of hyperinsulinism: percutaneous transhepatic portal and pancreatic vein catheterization with hormone assay. AJR Am J Roentgenol 1982; 139(2. :237-245.

267. Ingemansson S, Kuhl C, Larsson LI, Lunderquist A, Lundquist I. Localization of insulinomas and islet cell hyperplasias by pancreatic vein catheterization and insulin assay. Surg Gynecol Obstet 1978; 146(5. :724-734.

268. Katz LB, Aufses AH, Jr., Rayfield E, Mitty H. Preoperative localization and intraoperative

glucose monitoring in the management of patients with pancreatic insulinoma. Surg Gynecol Obstet 1986; 163(6. :509-512.

269. Vinik AI, Thompson N. Controversies in the management of Zollinger-Ellison syndrome. Ann Intern Med 1986; 105(6. :956-959.

270. Pasieka JL, McLeod MK, Thompson NW, Burney RE. Surgical approach to insulinomas. Assessing the need for preoperative localization. Arch Surg 1992; 127(4. :442-447.

271. Fajans SS, Floyd JC, Jr., Knopf RF. Benzothiadiazine suppression in insulin release from normal and abnormal islet celll tissue in man. Ann N Y.Acad Sci 45, 481. 1986.

272. Fajans SS, Floyd JC, Jr., Thiffault CA, Knopf RF, Harrison TS, Conn JW. Further studies on diazoxide suppression of insulin release from abnormal and normal islet tissue in man. Ann N Y Acad Sci 1968; 150(2. :261-280.

273. Ulbrecht JS, Schmeltz R, Aarons JH, Greene DA. Insulinoma in a 94-year-old woman: long-term therapy with verapamil. Diabetes Care 1986; 9(2. :186-188.

274. Blum I, Doron M, Laron Z, Atsmon A, Tiqva P. Prevention of hypoglycemic attacks by propranolol in a patient suffering from insulinoma. Diabetes 1975; 24(6. :535-537.

275. Schusdziarra V, Zyznar E, Rouiller D, Boden G, Brown JC, Arimura A et al. Splanchnic somatostatin: a hormonal regulator of nutrient homeostasis. Science 1980; 207(4430. :530-532.

276. Brodows RG, Campbell RG. Control of refractory fasting hypoglycemia in a patient with suspected insulinoma with diphenylhydantoin. J Clin Endocrinol Metab 1974; 38(1. :159-162.

277. Hofeldt FD, Dippe SE, Levin SR, Karam JH, Blum MR, Forsham PH. Effects of diphenlhydantoin upon glucose-induced insulin secretion in threee patients with insulinoma. Diabetes 23[Diabetes], 192. 1973.

278. Tsai ST, Eckhauser FE, Thompson NW, Strodel WE, Vinik AI. Perioperative use of long-acting somatostatin analog (SMS 201-995. in patients with endocrine tumors of the gastroenteropancreatic axis. Surgery 1986; 100(4. :788-795.

279. Osei K, O'Dorisio TM. Malignant insulinoma: effects of a somatostatin analog (compound 201-995. on serum glucose, growth, and gastro-entero-pancreatic hormones. Ann Intern Med 1985; 103(2. :223-225.

280. VERNER JV, MORRISON AB. Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 1958; 25(3. :374-380.

281. MURRAY JS, PATON RR, POPE CE. Pancreatic tumor associated with flushing and diarrhea. Report of a case. N Engl J Med 1961; 264:436-439.

282. PRIEST WM, ALEXANDER MK. Isletcell tumour of the pancreas with peptic ulceration, diarrhoea, and hypokalaemia. Lancet 1957; 273(7006. :1145-1147.

283. Matsumoto K, Peter JB, Schultze R, Hakin A, Frank P. Watery diarrhea and hypokalemia associated with pancreatic islet cell adenoma. Gastroenterology 52, 965. 1967.

284. Marks IN, Bank S, Louw JH. Islet cell tumor of the pancreas with reversible watery diarrhea and achylorhydraia. Gastroenterology 1967; 52(4. :695-708.

285. Kraft AR, Tompkins RK, Zollinger RM. Recognition and management of the diarrheal syndrome caused by nonbeta islet cell tumors of the pancreas. Am J Surg 1970; 119(2. :163-170.

286. VERNER JV, Morrison A. Endocrine pancreatic islet disease with diarrhea: report on a case due to diffuse hyperplasia of nonbeta islet tissue with a review of 54 additional cases. Arch Intern Med 25, 374. 1958.

287. Tatemoto K, Mutt V. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature 1980; 285(5764. :417-418.

288. Barbezat GO, Grossman MI. Intestinal secretion: stimulation by peptides. Science 1971; 174(7. :422-424.

289. Bloom SR, Polak JM. VIP measurement in distinguishing Verner-Morrison syndrome and pseudo Verner-Morrison syndrome. Clin Endocrinol (Oxf. 1976; 5 Suppl:223S-228S.

290. Go V, Korinik J. Effect of vasoactive intestinal polypeptide on hepatic glucose release. SI Said, editor. In Vasoactive Intestinal Peptides . 1982. New York: Raven.

291. Rambaud JC, Galian A, Scotto J, Hautefeuille P, Matuchansky C, Modigliani R et al. Pancreatic cholera (W.D.H.A. syndrome. . Histochemical and ultrastructural studies. Virchows Arch A Pathol Anat Histol 1975; 367(1. :35-45.

292. Said SI, Mutt V. Isolation from porcine-intestinal wall of a vasoactive octacosapeptide related to secretin and to glucagon. Eur J Biochem 1972; 28(2. :199-204.

293. Long RG, Bryant MG, Mitchell SJ, Adrian TE, Polak JM, Bloom SR. Clinicopathological study of pancreatic and ganglioneuroblastoma tumours secreting vasoactive intestinal polypeptide (vipomas. . Br Med J (Clin Res Ed. 1981; 282(6278. :1767-1771.

294. Blair AW, Ahmed S. Presacral vipoma in a 16-month-old child. Acta Paediatr Belg 1981; 34(2. :89-91.

295. Carson DJ, Glasgow JF, Ardill J. Watery diarrhoea and elevated vasoactive intestine polypeptide associated with a massive neurofibroma in early childhood. J R Soc Med 1980; 73(1. :69-72.

296. Ebeid AM, Murray PD, Fischer JE. Vasoative intestinal peptide and the watery diarrhea syndrome. Ann Surg 1978; 187(4. :411-416.

297. Iida Y, Nose O, Kai H, Okada A, Mori T, Lee PK et al. Watery diarrhoea with a vasoactive intestinal peptide-producing ganglioneuroblastoma. Arch Dis Child 1980; 55(12. :929-936.

298. Kaplan SJ, Holbrook CT, McDaniel HG, Buntain WL, Crist WM. Vasoactive intestinal peptide secreting tumors of childhood. Am J Dis Child 1980; 134(1. :21-24.

299. Kudo K, Kitajima S, Munakata H, Yagihashi S. WDHA syndrome caused by VIP-producing ganglioneuroblastoma. J Pediatr Surg 1982; 17(4. :426-428.

300. Modlin IM, Bloom SR. VIPomas and the watery diarrhoea syndrome. S Afr Med J 1978; 54(2. :53-56.

301. Tiedemann K, Long RG, Pritchard J, Bloom SR. Plasma vasoactive intestinal polypeptide and other regulatory peptides in children with neurogenic tumours. Eur J Pediatr 1981; 137(2. :147-150.

302. Tiedemann K, Pritchard J, Long R, Bloom SR. Intractable diarrhoea in a patient with vasoactive intestinal peptide-secreting neuroblastoma. Attempted control by somatostatin. Eur J Pediatr 1981; 137(2. :217-219.

303. Yamaguchi K, Abe K, Adachi I, Tanaka M, Ueda M, Oka Y et al. Clinical and hormonal aspects of the watery diarrhea-hypokalemia-achlorhydria (WDHA. syndrome due to vasoactive intestinal polypeptide (VIP. -producing tumor. Endocrinol Jpn 1980; 27 Suppl 1:79-86.

304. Wesley JR, Vinik AI, O'Dorisio TM, Glaser B, Fink A. A new syndrome of symptomatic cutaneous mastocytoma producing vasoactive intestinal polypeptide. Gastroenterology 1982; 82(5 Pt 1. :963-967.

305. Hamilton I, Reis L, Bilimoria S, Long RG. A renal vipoma. Br Med J 1980; 281(6251. :1323-1324.

306. Itoh N, Obato K, Yanaihara N, Okamoto H. Human preprovasoactive intestinal polypeptide contains a novel PHI 27-likke peptide PHM-27. Nature 304, 547. 1993.

307. Bloom S, Polak JM. VIPomas. In Vasoactive Intestinal Peptides [SI Said]. 1982.

308. Bloom S, Polak J. Glucagonomas, VIPomas and somatostatinomas. Baillieres Clin Endocrinol Metab 9, 285. 1980.

309. Modlin IM, Bloom SR, Mitchell S. Plasma vasoactive intestinal polypeptide (VIP. levels and intestinal ischaemia. Experientia 1978; 34(4. :535-536.

310. Modlin I, Mitchell S, Bloom S. The systemic release and pharmacokinetics of VIP. SR

Bloom, editor. In Gut Hormones . 1978. Edinburgh: Churchill Livingstone.

311. Bloom S, Polak J. Hormone profiles. SR Bloom, JM Polak, editors. In Gut Hormones . 1981. New York: Churchill Livingstone.

312. Said SI. Vasoactive intestinal polypeptide: elevated plasma and tissue levels in the watery-diarrhea syndrome due to pancreatic and other tumors. Trans Assoc Am Physicians 1975; 88:87-93.

313. Friesen SR. The development of endocrinopathies in the prospective screening of two families with multiple endocrine adenopathy, type I. World J Surg 1979; 3(6. :753-764.

314. McGavran MH, Unger RH, Recant L, Polk HC, Kilo C, Levin ME. A glucagon-secreting alpha-cell carcinoma of the pancreas. N Engl J Med 1966; 274(25. :1408-1413.

315. Grimelius L, Wilander E. Silver stains in the study of endocrine cells of the gut and pancreas. Invest Cell Pathol 1980; 3(1. :3-12.

316. Sweet RD. A dermatosis specifically associated with a tumour of pancreatic alpha cells. Br J Dermatol 1974; 90(3. :301-308.

317. Khandekar JD, Oyer D, Miller HJ, Vick NA. Neurologic involvement in glucagonoma syndrome: response to combination chemotherapy with 5-fluorouracil and streptozotocin. Cancer 1979; 44(6. :2014-2016.

318. Binnick AN, Spencer SK, Dennison WL, Jr., Horton ES. Glucagonoma syndrome. Report of two cases and literature review. Arch Dermatol 1977; 113(6. :749-754.

319. Holst JJ. Possible entries to the diagnosis of a glucagon-producing tumour. Scand J Gastroenterol Suppl 1979; 53:53-56.

320. Norton J, Kahan C, Schiebinger R, Gorschboth C, Brennan M. Acid deficiency and the skin rash associated with glucgonoma. Ann Intern Med 91, 213. 1979.

321. Unger RH, Orci L. Glucagon and the A Cell. Physiology and pathophysiology. N Engl J Med 304, 1575. 1981.

322. Hoitsma HF, Cuesta MA, Starink TM, Uttendorfsky-van der Putten HJ, van der Veen EA. Zinc deficiency syndrome versus glucagonoma syndrome. Arch Chir Neerl 1979; 31(3. :131-140.

323. Montenegro F, Lawrence GD, Macon W, Pass C. Metastatic glucagonoma. improvement after surgical debulking. Am J Surg 1980; 139(3. :424-427.

324. von Schenck H, Thorell JI, Berg J, Bojs G, Dymling JF, Hallengren B et al. Metabolic studies and glucagon gel filtration pattern before and after surgery in a case of glucagonoma

syndrome. Acta Med Scand 1979; 205(3. :155-162.

325. Marynick SP, Fagadau WR, Duncan LA. Malignant glucagonoma syndrome: response to chemotherapy. Ann Intern Med 1980; 93(3. :453-454.

326. Conlon JM. The glucagon-like polypeptides – order out of chaos? Diabetologia 1980; 18(2. :85-88.

327. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955; 142(4. :709-723.

328. Higgins GA, Recant L, Fischman AB. The glucagonoma syndrome: surgically curable diabetes. Am J Surg 1979; 137(1. :142-148.

329. Villar HV, Johnson DG, Lynch PJ, Pond GD, Smith PH. Pattern of immunoreactive glucagon in portal, arterial and peripheral plasma before and after removal of glucagonoma. Am J Surg 1981; 141(1. :148-152.

330. Vale W, Rivier C, Brown M. Regulatory peptides of the hypothalamus. Annu Rev Physiol 1977; 39:473-527.

331. Creutzfeldt W, Arnold R. Somatostatin and the stomach: exocrine and endocrine aspects. Metabolism 1978; 27(9 Suppl 1. :1309-1315.

332. Ganda OP, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel YC et al. “Somatostatinoma”: a somatostatin-containing tumor of the endocrine pancreas. N Engl J Med 1977; 296(17. :963-967.

333. Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. N Engl J Med 1979; 301(6. :285-292.

334. Larsson LI, Hirsch MA, Holst JJ, Ingemansson S, Kuhl C, Jensen SL et al. Pancreatic somatostatinoma. Clinical features and physiological implications. Lancet 1977; 1(8013. :666-668.

335. Crain ELJr, Thorn GW. Functioning pancreatic islet cell adenomas. Medicine 28, 427. 1949.

336. Fisher RS, Rock E, Levin G, Malmud L. Effects of somatostatin on gallbadder emptying. Gastroenterology 92, 885. 1983.

337. Axelrod L, Bush MA, Hirsch HJ, Loo SW. Malignant somatostatinoma: clinical features and metabolic studies. J Clin Endocrinol Metab 1981; 52(5. :886-896.

338. Penman E, Wass J, Besser AU, Rees LU. Somatostatin secretion by llung and thymic tumors. Clin Endocrinol (Oxf. 13, 613. 1980.

339. Boden G, Baile CA, McLaughlin CL, Matschinsky FM. Effects of starvation and obesity on somatostatin, insulin, and glucagon release from an isolated perfused organ system. Am J Physiol 1981; 241(3. :E215-E220.

340. Creutzfeldt W, Lankisch PG, Folsch E. Hemmung der Secetin und Cholezystokinin-Pankreozymin-induzierten Saft und Enzymescretion des Pancreas und der Gallenblasen-Kontraktion beim Menchen durch Somatostatin. Dtsch Med Wochenschr 100, 1135. 1975.

341. Schwartz TW. Atropine suppression test for pancreatic polypeptide. Lancet 1978; 2(8079. :43-44.

342. Bloom SR, Mortimer CH, Thorner MO, Besser GM, Hall R, Gomez-Pan A et al. Inhibition of gastrin and gastric-acid secretion by growth-hormone release-inhibiting hormone. Lancet 1974; 2(7889. :1106-1109.

343. Vinik A, Shapiro B., Thompson NW. Plasma gut hormone levels in 37 patients with pheochromocytomas. World J Surg 10, 593. 1985.

344. Bhathena S, Higgins G, Recant L. Glucagonoma and glucagonoma syndrome. R.H Unger, L Orci, editors. In Glucagon , 413. 1981. New York: Elsevier/North Holland.

345. Vinik A, Delbridge L, Moattari R, Cho K, Thompson N. Transhepatic portal vein cathereterization for localization of insulinomas: a ten-year experience. Surgery 109, 1-11. 1991.

346. Jensen RT, Gardner JD, Raufman JP, Pandol SJ, Doppman JL, Collen MJ. Zollinger-Ellison syndrome: current concepts and management. Ann Intern Med 1983; 98(1. :59-75.

347. Vinik A, Levitt N, Pirnstone B, Wagner L. Peripheral plasma somatostatin-like immunoreactive responses to insulin hypoglycemia and mixed meal in healthy subjects in non-insulin-dependent maturity-onset diabetes. J Clin Endocrinol Metab 52, 330. 1980.

348. Sano T, Kagawa N, Hizawa K. Demonstration of somatostatin productin in medullary carcinoma of they thyroid. Jpn.J Cancer Res 10, 221. 1980.

349. Saito S, Saito H, Matsumura M, Ishimaru K, Sano T. Molecular heterogeneity and biological activity of immunoreactive somatostatin in medullary carcinoma of the thyroid. J Clin Endocrinol Metab 1981; 53(6. :1117-1122.

350. Roos BA, Lindall AW, Ells 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(2. :187-194.

351. Ghose RR, Gupta SK. Oat cell carcinoma of bronchus presenting with somatostatinoma syndrome. Thorax 1981; 36(7. :550-551.

352. Jackson J, Raju U, Janakivamon N. Metastic pulmonary somatostatinoma presenting with diabetic ketoacidosis: clinical biochemical and morphologic characterization. Clin Res 34, 196A. 1986.

353. Berelowitz M, Szabo M, Barowsky HW, Arbel ER, Frohman LA. Somatostatin-like immunoactivity and biological activity is present in a human pheochromocytoma. J Clin Endocrinol Metab 1983; 56(1. :134-138.

354. Samols E, Weir GC, Ramseur R, Day JA, Patel YC. Modulation of pancreatic somatostatin by adrenergic and cholinergic agonism and by hyper- and hypoglycemic sulfonamides. Metabolism 1978; 27(9 Suppl 1. :1219-1221.

355. Pipeleers D, Couturier E, Gepts W, Reynders J, Somers G. Five cases of somatostatinoma: clinical heterogeneity and diagnostic usefulness of basal and tolbutamide-induced hypersomatostatinemia. J Clin Endocrinol Metab 1983; 56(6. :1236-1242.

356. Chance RE, Jones WE. Polypeptides from bovine, ovine, human, and porcine pancreas. US Patent Office 842, 63. 1974.

357. Kimmel JR, Pollock HG, Hazelwood RL. Isolation and characterization of chicken insulin. Endocrinology 1968; 83(6. :1323-1330.

358. Glaser B, Vinik A, Sive A. Evidence for extravagal cholinergic dependence of pancreatic polypeptide responses to beef ingestion in man (abstract. . Diabetes 28, 414. 1979.

359. Floyd JC, Jr., Vinik A, Glaser B. Pancreatic polypeptide. W.Waldhusi, editor. In Proceedings of the 10th Congress of the International Diabetes Federation , 490. 1979. Amsterdam: Excerpta Medica.

360. Glaser B, Vinik AI, Sive AA, Floyd JC, Jr. Plasma human pancreatic polypeptide responses to administered secretin: effects of surgical vagotomy, cholinergic blockade, and chronic pancreatitis. J Clin Endocrinol Metab 1980; 50(6. :1094-1099.

361. Greenberg GR, McCloy RF, Adrian TE, Chadwick VS, Baron JH, Bloom SR. Inhibition of pancreas and gallbladder by pancreatic polypeptide. Lancet 1978; 2(8103. :1280-1282.

362. Tomita T, Kimmel JR, Friesen SR, Mantz FA, Jr. Pancreatic polypeptide cell hyperplasia with and without watery diarrhea syndrome. J Surg Oncol 1980; 14(1. :11-20.

363. Bordi C, Togni R, Baetens D, Ravazzola M, Malaisse-Lagae F, Orci L. Human islet cell tumor storing pancreatic polypeptide: a light and electron microscopic study. J Clin Endocrinol Metab 1978; 46(2. :215-219.

364. Strodel WE, Vinik AI, Lloyd RV, Glaser B, Eckhauser FE, Fiddian-Green RG et al. Pancreatic polypeptide-producing tumors. Silent lesions of the pancreas? Arch Surg 1984; 119(5. :508-514.

365. Larsson LI, Schwartz T, Lundquist G. Pancreatic polypeptide in pancreatic endocrine tumors, possible implication in watery diarrhea syndrome. Am J Pathol 85, 675. 1976.

366. Larsson LI. Two distinct types of islet abnormalities associated with endocrine pancreatic tumours. Virchows Arch A Pathol Anat Histol 1977; 376(3. :209-219.

367. Polak JM, Bloom SR, Adrian TE, Heitz P, Bryant MG, Pearse AG. Pancreatic polypeptide in insulinomas, gastrinomas, vipomas, and glucagonomas. Lancet 1976; 1(7955. :328-330.

368. Lamers CB, Buis JT, van Tongeren J. Secretin-stimulated serum gastrin levels in hyperparathyroid patients from families with multiple endocrine adenomatosis type I. Ann Intern Med 1977; 86(6. :719-724.

369. Vinik A, Glaser B. Pancreatic endocrine tumors. In Pancreatic Disease [TL Dent], 427. 1981. New York: Grune & Stratton.

370. O'Dorisio T, Vinik A. Pancreatic polypeptide and mixed peptide-producing tumors of the gastrointestinal tract. S Cohen, RD Soloway, editors. In Contemporary Issues in Gastroenterology , 117. 1985. New York: Churchill-Livingstone.

371. Friesen SR, Kimmel JR, Tomita T. Pancreatic polypeptide as screening marker for pancreatic polypeptide apudomas in multiple endocrinopathies. Am J Surg 1980; 139(1. :61-72.

372. Carraway R, Leeman SE. The isolation of a new hypotensive peptide, neurotensin, from bovine hypothalami. J Biol Chem 1973; 248(19. :6854-6861.

373. Hammer RA, Leeman SE, Carraway R, Williams RH. Isolation of human intestinal neurotensin. J Biol Chem 1980; 255(6. :2476-2480.

374. Hammer R, Leeman S. Neurotensin: properties and actions. SR Bloom, JM Polak, editors. In Gut Hormones 2, 290. 1981. Edinburgh: Churchill Livingstone.

375. Mitchenere P, Adrian TE, Kirk RM, Bloom SR. Effect of gut regulatory peptides of intestinal luminal fluid in the rat. Life Sci 1981; 29(15. :1563-40.

376. Andersson S, Rosell S, Hjelmquist U, Chang D, Folkers K. Inhibition of gastric and intestinal motor activity in dogs by (Gln4. neurotensin. Acta Physiol Scand 1977; 100(2. :231-235.

377. Blackburn AM, Fletcher DR, Bloom SR, Christofides ND, Long RG, Fitzpatrick ML et al. Effect of neurotensin on gastric function in man. Lancet 1980; 1(8176. :987-989.

378. Carraway RE, Demers LM, Leeman SE. Hyperglycemic effect of neurotensin, a hypothalamic peptide. Endocrinology 1976; 99(6. :1452-1462.

379. Nagai K, Frohman LA. Hyperglycemia and hyperglucagonemia following neurotensin

administration. Life Sci 1976; 19(2. :273-279.

380. Polak JM, Sullivan SN, Bloom SR, Buchan AM, Facer P, Brown MR et al. Specific localisation of neurotensin to the N cell in human intestine by radioimmunoassay and immunocytochemistry. Nature 1977; 270(5633. :183-184.

381. Johnson J, Fabri PJ, Lott JA. Serum gastrins in Zollinger -Ellison syndrome-identification of localized disease. J Clin Endocrinol Metab 62, 970-974. 1980.

382. Blackburn AM, Bloom SR. A radioimmunoassay for neurotensin in human plasma. J Endocrinol 1979; 83(2. :175-181.

383. Besterman HS, Bloom SR, Sarson DL, Blackburn AM, Johnston DI, Patel HR et al. Gut-hormone profile in coeliac disease. Lancet 1978; 1(8068. :785-788.

384. Feurle GE, Helmstaedter V, Tischbirek K, Carraway R, Forssmann WG, Grube D et al. A multihormonal tumor of the pancreas producing neurotensin. Dig Dis Sci 1981; 26(12. :1125-1133.

385. Gutniak M, Rosenqvist U, Grimelius L, Lundberg JM, Hokfelt T, Rokaeus A et al. Report on a patient with watery diarrhoea syndrome caused by a pancreatic tumour containing neurotensin, enkephalin and calcitonin. Acta Med Scand 1980; 208(1-2. :95-100.

386. Maier W, Schumacher KA, Etzrodt H, Arlart I. An neurotensinoma of the head of the pancreas. Demonstration by ultrasound and computed tomography. Eur J Radiol 1982; 2(2. :125-127.

387. Shulkes A, Boden R, Cook I, Gallagher N, Furness JB. Characterization of a pancreatic tumor containing vasoactive intestinal peptide, neurotensin, and pancreatic polypeptide. J Clin Endocrinol Metab 1984; 58(1. :41-48.

388. Wood JR, Wood SM, Lee YC, Bloom SR. Neurotensin-secreting carcinoma of the bronchus. Postgrad Med J 1983; 59(687. :46-47.

389. Brown M, Vale W. Effects of neurotensin and substance P on plasma insulin, glucagon and glucose levels. Endocrinology 1976; 98(3. :819-822.

390. Yallow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest 39, 1157. 1960.

391. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402(6762. :656-660.

392. Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2000; 141(11. :4255-4261.

393. Tena-Sempere M, Barreiro ML, Gonzalez LC, Gaytan F, Zhang FP, Caminos JE et al. Novel expression and functional role of ghrelin in rat testis. Endocrinology 2002; 143(2. :717-725.

394. Mori K, Yoshimoto A, Takaya K, Hosoda K, Ariyasu H, Yahata K et al. Kidney produces a novel acylated peptide, ghrelin. FEBS Lett 2000; 486(3. :213-216.

395. Gualillo O, Caminos J, Blanco M, Garcia-Caballero T, Kojima M, Kangawa K et al. Ghrelin, a novel placental-derived hormone. Endocrinology 2001; 142(2. :788-794.

396. Korbonits M, Kojima M, Kangawa K, Grossman AB. Presence of ghrelin in normal and adenomatous human pituitary. Endocrine 2001; 14(1. :101-104.

397. Volante M, Papotti M, Gugliotta P, Migheli A, Bussolati G. Extensive DNA fragmentation in oxyphilic cell lesions of the thyroid. J Histochem Cytochem 2001; 49(8. :1003-1011.

398. Muccioli G, Tschop M, Papotti M, Deghenghi R, Heiman M, Ghigo E. Neuroendocrine and peripheral activities of ghrelin: implications in metabolism and obesity. Eur J Pharmacol 2002; 440(2-3. :235-254.

399. Hattori N, Saito T, Yagyu T, Jiang BH, Kitagawa K, Inagaki C. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. J Clin Endocrinol Metab 2001; 86(9. :4284-4291.

400. Tanaka M, Hayashida Y, Nakao N, Nakai N, Nakashima K. Testis-specific and developmentally induced expression of a ghrelin gene-derived transcript that encodes a novel polypeptide in the mouse. Biochim Biophys Acta 2001; 1522(1. :62-65.

401. Chapman IM, Hartman ML, Pezzoli SS, Thorner MO. Enhancement of pulsatile growth hormone secretion by continuous infusion of a growth hormone-releasing peptide mimetic, L-692,429, in older adults–a clinical research center study. J Clin Endocrinol Metab 1996; 81(8. :2874-2880.

402. Volante M, Fulcheri E, Allia E, Cerrato M, Pucci A, Papotti M. Ghrelin expression in fetal, infant, and adult human lung. J Histochem Cytochem 2002; 50(8. :1013-1021.

403. Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H et al. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. Diabetes 2002; 51(1. :124-129.

404. Egido EM, Rodriguez-Gallardo J, Silvestre RA, Marco J. Inhibitory effect of ghrelin on insulin and pancreatic somatostatin secretion. Eur J Endocrinol 2002; 146(2. :241-244.

405. Horvath TL, Diano S, Sotonyi P, Heiman M, Tschop M. Minireview: ghrelin and the regulation of energy balance–a hypothalamic perspective. Endocrinology 2001; 142(10. :4163-4169.

406. Kamegai J, Tamura H, Shimizu T, Ishii S, Sugihara H, Wakabayashi I. Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. Endocrinology 2000; 141(12. :4797-4800.

407. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z et al. Ghrelin stimulates gastric acid secretion and motility in rats. Biochem Biophys Res Commun 2000; 276(3. :905-908.

408. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature 2000; 407(6806. :908-913.

409. Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S et al. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. Endocrinology 2000; 141(11. :4325-4328.

410. Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T et al. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab 2001; 86(10. :4753-4758.

411. Date Y, Nakazato M, Murakami N, Kojima M, Kangawa K, Matsukura S. Ghrelin acts in the central nervous system to stimulate gastric acid secretion. Biochem Biophys Res Commun 2001; 280(3. :904-907.

412. Bednarek MA, Feighner SD, Pong SS, McKee KK, Hreniuk DL, Silva MV et al. Structure-function studies on the new growth hormone-releasing peptide, ghrelin: minimal sequence of ghrelin necessary for activation of growth hormone secretagogue receptor 1a. J Med Chem 2000; 43(23. :4370-4376.

413. Yoshihara F, Kojima M, Hosoda H, Nakazato M, Kangawa K. Ghrelin: a novel peptide for growth hormone release and feeding regulation. Curr Opin Clin Nutr Metab Care 2002; 5(4. :391-395.

414. Wierup N, Svensson H, Mulder H, Sundler F. The ghrelin cell: a novel developmentally regulated islet cell in the human pancreas. Regul Pept 2002; 107(1-3. :63-69.

415. Tolle V, Bassant MH, Zizzari P, Poindessous-Jazat F, Tomasetto C, Epelbaum J et al. Ultradian rhythmicity of ghrelin secretion in relation with GH, feeding behavior, and sleep-wake patterns in rats. Endocrinology 2002; 143(4. :1353-1361.

416. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001; 50(8. :1714-1719.

417. Saad MF, Bernaba B, Hwu CM, Jinagouda S, Fahmi S, Kogosov E et al. Insulin regulates plasma ghrelin concentration. J Clin Endocrinol Metab 2002; 87(8. :3997-4000.

418. Pagotto U, Gambineri A, Vicennati V, Heiman ML, Tschop M, Pasquali R. Plasma ghrelin, obesity, and the polycystic ovary syndrome: correlation with insulin resistance and androgen levels. J Clin Endocrinol Metab 2002; 87(12. :5625-5629.

419. Broglio F, Arvat E, Benso A, Gottero C, Muccioli G, Papotti M et al. Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. J Clin Endocrinol Metab 2001; 86(10. :5083-5086.

420. Svensson J, Lonn L, Jansson JO, Murphy G, Wyss D, Krupa D et al. Two-month treatment of obese subjects with the oral growth hormone (GH. secretagogue MK-677 increases GH secretion, fat-free mass, and energy expenditure. J Clin Endocrinol Metab 1998; 83(2. :362-369.

421. Chapman IM, Pescovitz OH, Murphy G, Treep T, Cerchio KA, Krupa D et al. Oral administration of growth hormone (GH. releasing peptide-mimetic MK-677 stimulates the GH/insulin-like growth factor-I axis in selected GH-deficient adults. J Clin Endocrinol Metab 1997; 82(10. :3455-3463.

422. Muller AF, Janssen JA, Hofland LJ, Lamberts SW, Bidlingmaier M, Strasburger CJ et al. Blockade of the growth hormone (GH. receptor unmasks rapid GH-releasing peptide-6-mediated tissue-specific insulin resistance. J Clin Endocrinol Metab 2001; 86(2. :590-593.

423. Nakagawa E, Nagaya N, Okumura H, Enomoto M, Oya H, Ono F et al. Hyperglycaemia suppresses the secretion of ghrelin, a novel growth-hormone-releasing peptide: responses to the intravenous and oral administration of glucose. Clin Sci (Lond. 2002; 103(3. :325-328.

424. Lucidi P, Murdolo G, Di Loreto C, De Cicco A, Parlanti N, Fanelli C et al. Ghrelin is not necessary for adequate hormonal counterregulation of insulin-induced hypoglycemia. Diabetes 2002; 51(10. :2911-2914.

425. Volante M, Allia E, Gugliotta P, Funaro A, Broglio F, Deghenghi R et al. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. J Clin Endocrinol Metab 2002; 87(3. :1300-1308.

426. Papotti M, Cassoni P, Volante M, Deghenghi R, Muccioli G, Ghigo E. Ghrelin-producing endocrine tumors of the stomach and intestine. J Clin Endocrinol Metab 2001; 86(10. :5052-5059.

427. Iwakura H, Hosoda K, Doi R, Komoto I, Nishimura H, Son C et al. Ghrelin expression in islet cell tumors: augmented expression of ghrelin in a case of glucagonoma with multiple endocrine neoplasm type I. J Clin Endocrinol Metab 2002; 87(11. :4885-4888.

428. Corbetta S, Peracchi M, Cappiello V, Lania A, Lauri E, Vago L et al. Circulating ghrelin levels in patients with pancreatic and gastrointestinal neuroendocrine tumors: identification of one pancreatic ghrelinoma. J Clin Endocrinol Metab 2003; 88(7. :3117-3120.

429. Reichlin S. Somatostatin. N Engl J Med 1983; 309(24. :1495-1501.

430. Reichlin S. Somatostatin (second of two parts. . N Engl J Med 1983; 309(25. :1556-1563.

431. Schally AV. Oncological applications of somatostatin analogues. Cancer Res 1988; 48(24 Pt 1. :6977-6985.

432. Lamberts SW, Krenning EP, Reubi JC. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. Endocr Rev 1991; 12(4. :450-482.

433. Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ. Octreotide. N Engl J Med 1996; 334(4. :246-254.

434. Hoyer D, Lubbert H, Bruns C. Molecular pharmacology of somatostatin receptors. Naunyn Schmiedebergs Arch Pharmacol 1994; 350(5. :441-453.

435. Patel YC. Molecular pharmacology of somatostatin receptor subtypes. J Endocrinol Invest 1997; 20(6. :348-367.

436. Vanetti M, Kouba M, Wang X, Vogt G, Hollt V. Cloning and expression of a novel mouse somatostatin receptor (SSTR2B. . FEBS Lett 1992; 311(3. :290-294.

437. Bell GI, Yasuda K, Kong H, Law SF, Raynor K, Reisine T. Molecular biology of somatostatin receptors. Ciba Found Symp 1995; 190:65-79.

438. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol 1999; 20(3. :157-198.

439. Reubi JC, Kappeler A, Waser B, Laissue J, Hipkin RW, Schonbrunn A. Immunohistochemical localization of somatostatin receptors sst2A in human tumors. Am J Pathol 1998; 153(1. :233-245.

440. Kumar U, Sasi R, Suresh S, Patel A, Thangaraju M, Metrakos P et al. Subtype-selective expression of the five somatostatin receptors (hSSTR1-5. in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. Diabetes 1999; 48(1. :77-85.

441. Reubi JC, Krenning E, Lamberts SW, Kvols L. In vitro detection of somatostatin receptors in human tumors. Metabolism 1992; 41(9 Suppl 2. :104-110.

442. Reubi JC, Laissue J, Krenning E, Lamberts SW. Somatostatin receptors in human cancer: incidence, characteristics, functional correlates and clinical implications. J Steroid Biochem Mol Biol 1992; 43(1-3. :27-35.

443. Reubi JC, Laissue J, Waser B, Horisberger U, Schaer JC. Expression of somatostatin receptors in normal, inflamed, and neoplastic human gastrointestinal tissues. Ann N Y Acad Sci 1994; 733:122-137.

444. Reubi JC, Schaer JC, Laissue JA, Waser B. Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels. Metabolism 1996; 45(8 Suppl 1. :39-41.

445. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001; 28(7. :836-846.

446. Vikic-Topic S, Raisch KP, Kvols LK, Vuk-Pavlovic S. Expression of somatostatin receptor subtypes in breast carcinoma, carcinoid tumor, and renal cell carcinoma. J Clin Endocrinol Metab 1995; 80(10. :2974-2979.

447. Panetta R, Patel YC. Expression of mRNA for all five human somatostatin receptors (hSSTR1-5. in pituitary tumors. Life Sci 1995; 56(5. :333-342.

448. Schulz S, Schulz S, Schmitt J, Wiborny D, Schmidt H, Olbricht S et al. Immunocytochemical detection of somatostatin receptors sst1, sst2A, sst2B, and sst3 in paraffin-embedded breast cancer tissue using subtype-specific antibodies. Clin Cancer Res 1998; 4(9. :2047-2052.

449. Kimura N, Pilichowska M, Date F, Kimura I, Schindler M. Immunohistochemical expression of somatostatin type 2A receptor in neuroendocrine tumors. Clin Cancer Res 1999; 5(11. :3483-3487.

450. Hofland LJ, Breeman WA, Krenning EP, de Jong M, Waaijers M, van Koetsveld PM et al. Internalization of [DOTA degrees,125I-Tyr3]Octreotide by somatostatin receptor-positive cells in vitro and in vivo: implications for somatostatin receptor-targeted radio-guided surgery. Proc Assoc Am Physicians 1999; 111(1. :63-69.

451. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. Eur J Nucl Med Mol Imaging 2003; 30(5. :781-793.

452. de Herder WW, Hofland LJ, van der Lely AJ, Lamberts SW. Peptide receptors in gut endocrine tumours. Baillieres Clin Gastroenterol 1996; 10(4. :571-587.

453. Papotti M, Bongiovanni M, Volante M, Allia E, Landolfi S, Helboe L et al. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch 2002; 440(5. :461-475.

454. de Herder WW, Lamberts SW. Somatostatin and somatostatin analogues: diagnostic and therapeutic uses. Curr Opin Oncol 2002; 14(1. :53-57.

455. Krenning EP, Kwekkeboom DJ, Oei HY, Reubi JC, van Hagen PM, Kooij PP et al. Somatostatin receptor imaging of endocrine gastrointestinal tumors. Schweiz Med Wochenschr 1992; 122(17. :634-637.

456. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY et al. Somatostatin receptor scintigraphy with {111 IN-DTPA-D-Phe1]- and [123I-Tyr3]- octreotide: the Rotterdam experience with moree than 1000 patients. European Journal of Nuclear Medicine 20, 716-731. 2003. Ref Type: Electronic Citation

457. Krenning EP, Valkema R, Kooij PP, Breeman WA, Bakker WH, deHerder WW et al. Scintigraphy and radionuclide therapy with [indium-111-labelled-diethyl triamine penta-acetic acid-D-Phe1]-octreotide. Ital J Gastroenterol Hepatol 1999; 31 Suppl 2:S219-S223.

458. Kwekkeboom DJ, Krenning EP, Bakker WH, Oei HY, Kooij PP, Lamberts SW. Somatostatin analogue scintigraphy in carcinoid tumours. Eur J Nucl Med 1993; 20(4. :283-292.

459. Kwekkeboom DJ, Krenning EP. Somatostatin receptor scintigraphy in patients with carcinoid tumors. World J Surg 1996; 20(2. :157-161.

460. Rocheville M, Lange DC, Kumar U, Patel SC, Patel RC, Patel YC. Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. Science 2000; 288(5463. :154-157.

461. Rocheville M, Lange DC, Kumar U, Sasi R, Patel RC, Patel YC. Subtypes of the somatostatin receptor assemble as functional homo- and heterodimers. J Biol Chem 2000; 275(11. :7862-7869.

462. Bauer W, Briner U, Doepfner W, Haller R, Huguenin R, Marbach P et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31(11. :1133-1140.

463. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. J Clin Oncol 1987; 5(10. :1502-1522.

464. Ben Yosef R, Glaser B, Catane R. [Somatostatin analogue in the treatment of neuroendocrine gut tumors]. Harefuah 1990; 119(1-2. :15-18.

465. Hofland LJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr Rev 2003; 24(1. :28-47.

466. Dunne M, Elton R, Fletcher T, Hofker P, Shul J. Sandostatin and gastroenteropancreatic tumors-therapeutic characteristics. TM O'Dorisio, editor. In Sandostatin in the Treatment of GEP Endocrine Tumors , 93. 1987. Berlin: Springer Verlag. Ref Type: Electronic Citation

467. Moattari A, Cho K, Vinik A. Sandostatin in treatment of co-existing glucagonoma and pancreatic pseudocyst dissociation of responses. Surgery 108, 581. 1980. Ref Type: Electronic Citation

468. Koelz A, Kraenzlin M, Gyr K. Escape of the response to a long-acting somatostatin analogue (Sandostatin. in patients with VIPoma. Gastroenterology 92, 527. 1987. Ref Type:

Electronic Citation

469. Dunnick NR, Doppman JL, Mills SR, McCarthy DM. Computed tomographic detection of nonbeta pancreatic islet cell tumors. Radiology 1980; 135(1. :117-120.

470. Vinik AI, Thompson N, Eckhauser F, Moattari AR. Clinical features of carcinoid syndrome and the use of somatostatin analogue in its management. Acta Oncol 1989; 28(3. :389-402.

471. Buscail L, Delesque N, Esteve JP, Saint-Laurent N, Prats H, Clerc P et al. Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin analogues: mediation by human somatostatin receptor subtypes SSTR1 and SSTR2. Proc Natl Acad Sci U S A 1994; 91(6. :2315-2319.

472. Buscail L, Esteve JP, Saint-Laurent N, Bertrand V, Reisine T, O'Carroll AM et al. Inhibition of cell proliferation by the somatostatin analogue RC-160 is mediated by somatostatin receptor subtypes SSTR2 and SSTR5 through different mechanisms. Proc Natl Acad Sci U S A 1995; 92(5. :1580-1584.

473. Cordelier P, Esteve JP, Bousquet C, Delesque N, O'Carroll AM, Schally AV et al. Characterization of the antiproliferative signal mediated by the somatostatin receptor subtype sst5. Proc Natl Acad Sci U S A 1997; 94(17. :9343-9348.

474. Alderton F, Fan TP, Schindler M, Humphrey PP. Rat somatostatin sst2(a. and sst2(b. receptor isoforms mediate opposite effects on cell proliferation. Br J Pharmacol 1998; 125(8. :1630-1633.

475. Bousquet C, Delesque N, Lopez F, Saint-Laurent N, Esteve JP, Bedecs K et al. sst2 somatostatin receptor mediates negative regulation of insulin receptor signaling through the tyrosine phosphatase SHP-1. J Biol Chem 1998; 273(12. :7099-7106.

476. Bousquet C, Puente E, Buscail L, Vaysse N, Susini C. Antiproliferative effect of somatostatin and analogs. Chemotherapy 2001; 47 Suppl 2:30-39.

477. Sharma K, Srikant CB. Induction of wild-type p53, Bax, and acidic endonuclease during somatostatin-signaled apoptosis in MCF-7 human breast cancer cells. Int J Cancer 1998; 76(2. :259-266.

478. Pages P, Benali N, Saint-Laurent N, Esteve JP, Schally AV, Tkaczuk J et al. sst2 somatostatin receptor mediates cell cycle arrest and induction of p27(Kip1. . Evidence for the role of SHP-1. J Biol Chem 1999; 274(21. :15186-15193.

479. Rochaix P, Delesque N, Esteve JP, Saint-Laurent N, Voight JJ, Vaysse N et al. Gene therapy for pancreatic carcinoma: local and distant antitumor effects after somatostatin receptor sst2 gene transfer. Hum Gene Ther 1999; 10(6. :995-1008.

480. Benali N, Cordelier P, Calise D, Pages P, Rochaix P, Nagy A et al. Inhibition of growth and

metastatic progression of pancreatic carcinoma in hamster after somatostatin receptor subtype 2 (sst2. gene expression and administration of cytotoxic somatostatin analog AN-238. Proc Natl Acad Sci U S A 2000; 97(16. :9180-9185.

481. Vernejoul F, Faure P, Benali N, Calise D, Tiraby G, Pradayrol L et al. Antitumor effect of in vivo somatostatin receptor subtype 2 gene transfer in primary and metastatic pancreatic cancer models. Cancer Res 2002; 62(21. :6124-6131.

482. Vinik AI, Tsai ST, Moattari AR, Cheung P, Eckhauser FE, Cho K. Somatostatin analogue (SMS 201-995. in the management of gastroenteropancreatic tumors and diarrhea syndromes. Am J Med 1986; 81:23-40.

483. Cho K, Vinik A. Effect of somatostatin analogue 201-995 on blood flow to endocrine tumors. Radiological Society of North America 1987.

484. Kraenzlin ME, Ch'ng JC, Wood SM, Bloom SR. Can inhibition of hormone secretion be associated with endocrine tumour shrinkage? Lancet 1983; 2(8365-66. :1501.

485. Clements D, Elias E. Regression of metastatic vipoma with somatostatin analogue SMS 201-995. Lancet 1985; 1(8433. :874-875.

486. Wiedenmann B, Rath U, Radsch R, Becker F, Kommerell B. Tumor regression of an ileal carcinoid under the treatment with the somatostatin analogue SMS 201-995. Klin Wochenschr 1988; 66(2. :75-77.

487. Woltering EA, Watson JC, Alperin-Lea RC, Sharma C, Keenan E, Kurozawa D et al. Somatostatin analogs: angiogenesis inhibitors with novel mechanisms of action. Invest New Drugs 1997; 15(1. :77-86.

488. Filosso PL, Croce S, Oliaro A, Ruffini E. Long-term survival of patients treated with octreotide for metastatic well differentiated neuroendocrine carcinoma of the lung. J Cardiovasc Surg (Torino. 2000; 41(5. :773-776.

489. Imtiaz KE, Monteith P, Khaleeli A. Complete histological regression of metastatic carcinoid tumour after treatment with octreotide. Clin Endocrinol (Oxf. 2000; 53(6. :755-758.

490. Fave GD, Corleto VD. Oncogenes, growth factors, receptor expression and proliferation markers in digestive neuroendocrine tumours. A critical reappraisal. Ann Oncol 2001; 12 Suppl 2:S13-S17.

491. Garcia dlT, Wass JA, Turner HE. Antiangiogenic effects of somatostatin analogues. Clin Endocrinol (Oxf. 2002; 57(4. :425-441.

492. Florio T, Morini M, Villa V, Arena S, Corsaro A, Thellung S et al. Somatostatin inhibits tumor angiogenesis and growth via somatostatin receptor-3-mediated regulation of endothelial nitric oxide synthase and mitogen-activated protein kinase activities. Endocrinology 2003;

144(4. :1574-1584.

493. Krenning EP, Bakker WH, Breeman WA, Koper JW, Kooij PP, Ausema L et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet 1989; 1(8632. :242-244.

494. Krenning EP, Kwekkeboom DJ, Oei HY, de Jong RJ, Dop FJ, Reubi JC et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann N Y Acad Sci 1994; 733:416-424.

495. Virgolini I, Patri P, Novotny C, Traub T, Leimer M, Fuger B et al. Comparative somatostatin receptor scintigraphy using in-111-DOTA-lanreotide and in-111-DOTA-Tyr3-octreotide versus F-18-FDG-PET for evaluation of somatostatin receptor-mediated radionuclide therapy. Ann Oncol 2001; 12 Suppl 2:S41-S45.

496. Vinik A, Perry R. Neoplasms of the Gastroenteropancreatic Endocrine System. Cancer Medicine 2001; 4th Edition:1605-1639.

497. Granberg D, Sundin A, Janson ET, Oberg K, Skogseid B, Westlin JE. Octreoscan in patients with bronchial carcinoid tumours. Clin Endocrinol (Oxf. 2003; 59(6. :793-799.

498. Vinik AI, Tsai S, Moattari AR, Cheung P. Somatostatin analogue (SMS 201-995. in patients with gastrinomas. Surgery 1988; 104(5. :834-842.

499. Hausdorff WP, Caron MG, Lefkowitz RJ. Turning off the signal: desensitization of beta-adrenergic receptor function. FASEB J 1990; 4(11. :2881-2889.

500. Yu SS, Lefkowitz RJ, Hausdorff WP. Beta-adrenergic receptor sequestration. A potential mechanism of receptor resensitization. J Biol Chem 1993; 268(1. :337-341.

501. Roettger BF, Rentsch RU, Pinon D, Holicky E, Hadac E, Larkin JM et al. Dual pathways of internalization of the cholecystokinin receptor. J Cell Biol 1995; 128(6. :1029-1041.

502. Ferguson SS, Barak LS, Zhang J, Caron MG. G-protein-coupled receptor regulation: role of G-protein-coupled receptor kinases and arrestins. Can J Physiol Pharmacol 1996; 74(10. :1095-1110.

503. Koenig JA, Edwardson JM. Endocytosis and recycling of G protein-coupled receptors. Trends Pharmacol Sci 1997; 18(8. :276-287.

504. Janson ET, Westlin JE, Ohrvall U, Oberg K, Lukinius A. Nuclear localization of 111In after intravenous injection of [111In-DTPA-D-Phe1]-octreotide in patients with neuroendocrine tumors. J Nucl Med 2000; 41(9. :1514-1518.

505. Anthony LB, Woltering EA, Espenan GD, Cronin MD, Maloney TJ, McCarthy KE. Indium-111-pentetreotide prolongs survival in gastroenteropancreatic malignancies. Semin Nucl

Med 2002; 32(2. :123-132.

506. Kwekkeboom D, Kam B, Bakker W, Kooij P, de Herder W, Srinivasan S et al. Treatment with Lu-177-DOTA-Tyr3-octreotate in patients with somatostatiin receptor positive tumors . Journal of Nuclear Medicine 43[Suppl 5], 34P. 2002. Ref Type: Electronic Citation

507. Kwekkeboom DJ, Bakker WH, Kam BL, Teunissen JJ, Kooij PP, de Herder WW et al. Treatment of patients with gastro-entero-pancreatic (GEP. tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0. ,Tyr3]octreotate. Eur J Nucl Med Mol Imaging 2003; 30(3. :417-422.

508. Valkema R, de Jong M, Bakker WH, Breeman WA, Kooij PP, Lugtenburg PJ et al. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. Semin Nucl Med 2002; 32(2. :110-122.

509. Virgolini I, Britton K, Buscombe J, Moncayo R, Paganelli G, Riva P. In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. Semin Nucl Med 2002; 32(2. :148-155.

510. Nouel D, Gaudriault G, Houle M, Reisine T, Vincent JP, Mazella J et al. Differential internalization of somatostatin in COS-7 cells transfected with SST1 and SST2 receptor subtypes: a confocal microscopic study using novel fluorescent somatostatin derivatives. Endocrinology 1997; 138(1. :296-306.

511. Hukovic N, Rocheville M, Kumar U, Sasi R, Khare S, Patel YC. Agonist-dependent up-regulation of human somatostatin receptor type 1 requires molecular signals in the cytoplasmic C-tail. J Biol Chem 1999; 274(35. :24550-24558.

512. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF. receptor binding and a unique antisecretory profile. Eur J Endocrinol 2002; 146(5. :707-716.

513. Weckbecker G, Briner U, Lewis I, Bruns C. SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. Endocrinology 2002; 143(10. :4123-4130.

514. Pfeiffer M, Koch T, Schroder H, Klutzny M, Kirscht S, Kreienkamp HJ et al. Homo- and heterodimerization of somatostatin receptor subtypes. Inactivation of sst(3. receptor function by heterodimerization with sst(2A. . J Biol Chem 2001; 276(17. :14027-14036.

515. Pfeiffer M, Koch T, Schroder H, Laugsch M, Hollt V, Schulz S. Heterodimerization of somatostatin and opioid receptors cross-modulates phosphorylation, internalization, and desensitization. J Biol Chem 2002; 277(22. :19762-19772.

516. Mawrin C, Schulz S, Pauli SU, Treuheit T, Diete S, Dietzmann K et al. Differential expression of sst1, sst2A, and sst3 somatostatin receptor proteins in low-grade and high-grade

astrocytomas. J Neuropathol Exp Neurol 2004; 63(1. :13-19.

517. Qin RY, Fang RL, Gupta MK, Liu ZR, Wang DY, Chang Q et al. Alteration of somatostatin receptor subtype 2 gene expression in pancreatic tumor angiogenesis. World J Gastroenterol 2004; 10(1. :132-135.

518. Rubello D, Rufini V, De Carlo E, Martini C, Calcagni ML, Sicolo N et al. New perspectives in diagnosis and therapy of endocrine gastroenteropancreatic (GEP. tumors with somatosatin analogues. Minerva Endocrinol 28[4], 259-296. 2003. Ref Type: Electronic Citation

519. Faiss S, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors–the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003; 21(14. :2689-2696.

520. Ajani JA, Kavanaugh J, Patt Y. Roferon and doxorubicin combination active against advanced islet cell or carcinoid tumors. Proc Am Assoc Cancer Res 30, 293. 1989. Ref Type: Electronic Citation

521. Marlink RG, Lokich JJ, Robins JR, Clouse ME. Hepatic arterial embolization for metastatic hormone-secreting tumors. Technique, effectiveness, and complications. Cancer 1990; 65(10. :2227-2232.

522. Broder LE, Carter SK. Pancreatic islet cell carcinoma. II. Results of therapy with streptozotocin in 52 patients. Ann Intern Med 1973; 79(1. :108-118.

523. Moertel C, Hanley J, Johnson L. Streptozotocin alone compared with streptoxocin plus fluoracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 303, 1189. 1980. Ref Type: Electronic Citation

524. Murray-Lyon I, Eddleston A, Williams R. Treatment of multiple hormone producing malignant islet cell tumour with streptozotcin. Lancet 2, 895. 1968. Ref Type: Electronic Citation

525. Schein P, Kahn R, Gorden P, Wells S, De Vita V. Streptozotocin for malignant insulinomas and carcinoid tumors. Arch Intern Med 132, 555. 1973. Ref Type: Electronic Citation

526. Friesen SR. Update on the diagnosis and treatment of rare neuroendocrine tumors. Surg Clin North Am 1987; 67(2. :379-393.

527. Bukowski RM, McCracken JD, Balcerzak SP, Fabian CJ. Phase II study of chlorozotocin in islet cell carcinoma. A southwest Oncology Group study. Cancer Chemother Pharmacol 1983; 11(1. :48-50.

528. Moertel CG, Lavin PT, Hahn RG. Phase II trial of doxorubicin therapy for advanced islet cell carcinoma. Cancer Treat Rep 1982; 66(7. :1567-1569.

529. Hahn RG, Caan A, Kessinger A. A phase II study of DTIC in the treatment of nonresectable islet cell carcinoma: an ECOG treatment protocol. Proceeding of Annual Meeting, American Society of Clinical Oncology.Proc Am Soc clin Oncol , A417. 1990. Ref Type: Electronic Citation

530. Saltz L, Lauwers G, Wiseberg J, Kelsen D. A phase II trial of carboplatin in patients with advanced APUD tumors. Cancer 1993; 72(2. :619-622.

531. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326(8. :519-523.

532. Eriksson B, Oberg K. An update of the medical treatment of malignant endocrine pancreatic tumors. Acta Oncol 1993; 32(2. :203-208.

533. Oberg K, Eriksson B, Janson ET. The clinical use of interferons in the management of neuroendocrine gastroenteropancreatic tumors. Ann N Y Acad Sci 1994; 733:471-478.