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FROM THE DEPARTMENT OF INTERNAL MEDICINE, DIVISION OF ENDOCRINOLOGY, AND THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF MICHIGAN MEDICAL CENTER, ANN ARBOR, MI 48109, USA.

CLINICAL FEATURES OF CARCINOID SYNDROME AND THE USE OF SOMATOSTATIN ANALOGUE IN ITS MANAGEMENT

A. I. VINIK, N. THOMPSON, F. ECKHAUSER and A. R. MOATTARI

Abstract

A review is given on the clinical features of carcinoid syndrome including symtomatology, diagnostics, biochemistry and treatment. We have reviewed the literature on current therapy of carcinoid patients with special emphasis on the use of the somatostatin analogue SMS 20-1995. In addition, we present data on the effects of SMS 201-995 on indices of a clinical, biochemical and tumor growth. Diarrhea is abolished or significantly reduced in 75% of patients, flushing improves in 100%, wheezing in 100% with a decrease in airways resistance, and in one patient myopathy has improved. Blood serotonin is notoriously resistant to intervention and urinary 5-HIAA will decrease in 75% of causes but subsequently rebounds in 38%. Tumors, in general, continue to grow, but this may be slowed or in rare cases tumor growth is arrested. In individual instances the tumor may even infarct, leading to spontaneous cure. Tumors secreting PP, ACTH and calcitonin may be particularly resistant to treatment, whereas VIP secreting tumors appear to be sensitive.

Key words: Carcinoid syndrome, clinical features, somatostatin analogue.

Carcinoids are the most common gut endocrine tumors. Of all GEP tumors, carcinoids account for 55%, insulinomas 17%, tumors of unknown types in 15%, gastrinomas 9%, vipomas 2% and the remainder 2%. The incidence of these tumors is around 1.5 cases per 100000 of the general population, accounting for 13–34% of all tumors of the small bowel and 17–46% of all malignant tumors of the small bowel (1). They derive from a primitive stem cell and are generally found in the gut wall. They frequently metastasize to the regional lymph nodes and the liver. The likelihood of metastases is related to tumor size. If less than 1 cm, the incidence of metastases is less than 2% but rises to 100% with tumors greater than 2 cm in diameter. The carcinoid syndrome (2) occurs in less than 10% of patients with tumors, and is especially common in tumors of the ileum and jejunum, but also occurs with bronchial, ovarian and other carcinoids (3).

Incidence. At the University of Michigan in the years 1959–1981, 92 cases were encountered or approximately 4 per year and between 1981–1988, 89 new cases or approximately 12 per year. In reviewing the reported world series of clinical compared with autopsy cases, the clinical experience was of a predominance of carcinoids in the appendix, presumably found by accident due to incidental appendectomy during other surgical procedures. In contrast, at autopsy carcinoid tumors are found in the jejunoileum where they have maintained an unobstrusive coexistence during life. Table 1 contrasts differences in clinical and autopsy material.

Table 1 shows the anatomic distribution of carcinoid tumors in world series and compares that in Fig. 1 with the changing pattern of carcinoid tumors in the last decade. In comparing our observations of this decade with those of the previous 2 certain notable differences are readily apparent as shown in Fig. 1.

Of note is the marked increase in the diagnosis of foregut carcinoids, notably that of the bronchus. While this may relate to a real increase in the prevalence of foregut carcinoids, the likelihood is that many such tumors were misdiagnosed as small cell carcinomas and with the advent of improved means of histochemical identification with the use of neurone specific enolase and chromogranin, that many of these hibitor forms 'small cell' carcinomas have now been diagnosed as bonafide carcinoid tumors. To be noted are the major differences in carcinoid tumors found in the jejunoileum in the autopsy versus the clinical series indicating that the tumor is not infrequently silent. In contrast is the 12-fold greater incidence of appendicial carcinoids in clinical cases suggesting that the obstruction of the appendix and presentation

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with abdominal pain of appendicitis may alert one to the presence of small tumors in the site.

Classification of carcinoids. One of the more useful ways of classifying carcinoid tumors has been according to the division of the primitive gut from which these cells arise. They may, thus, be divided into foregut tumors which include bronchus, stomach, the first portion of the duodenum and the pancreas, midgut tumors which derive from the second portion of the duodenum, the jejunoileum and right colon and hindgut tumors which include the transverse colon, left colon and rectum. This distinction assists in distinguishing a number of important biochemical and clinical differences between carcinoid tumors. Table 2 lists the many differences in the presentations of these tumors.

The foregut varieties, for example, are argentaffin negative. They have a low content of serotonin (5-hydroxytryptamine, 5-HT). They often secrete the serotonin precursor, 5-hydroxytryptophan (5-HTP) and histamine and a multitude of polypeptide hormones. Their functional manifestations include atypical carcinoid syndrome, Zollinger-Ellison syndrome, acromegaly, Cushing's, and a number of other endocrine disorders. They are, furthermore, unusual in that the flush which occurs tends to be of protracted duration, is often of a purplish (violaceous hue) rather than the usual pink/red color, and frequently leaves permanent telangiectasia and hypertrophy of the skin of the face and upper neck which assumes a leonine characteristic. It is not unusual for these tumors to metastasize to bone. In contrast, midgut carcinoids or argentaffin positive have a high 5-HT content, rarely secrete 5-HTP and often produce a number of other vasoactive compounds, such as kinins, prostaglandins, substance P and the clinical syndrome that derives is the classic carcinoid. These tumors rarely produce ACTH and very infrequently metastasize to bone. The hindgut tumors are argentaffin negative, rarely contain 5-HT, rarely secrete 5-HTP or other peptides, are usually silent in their presentation but may metastasize to bone.

Although carcinoids are classically tumors of enterochromaffin and argentaffin cells of the digestive tract, the term 'carcinoid tumor' can be expanded to cover 'gut' tumors of paracrine and endocrine-like cells of unknown function (4, 5). It is now established that these tumors are of neuroendocrine origin and derive from a primitive stem cell that may differentiate into any one of a variety of adult endocrine secreting cells: B cell and insulinoma; A cell and glucagonoma: D cell and somatostatinoma: and the PP cell and PPoma, or cells capable of producing ACTH, growth hormone releasing hormone (GHRH), VIP, substance P, gastrin releasing factor (GRF), calcitonin, and the EC cell with its ability to co-secrete amines, such as serotonin and the peptide motilin. This proposed evolutionary development is outlined in Fig. 1. At any one point in time, these cells may secrete one humor, whereas at other times the peptide or amine secreted may differ and yield an entirely different clinical syndrome. Indeed, metastases are known to secrete hormones that differ from the parent tumor and different metastases may secrete different hormones.

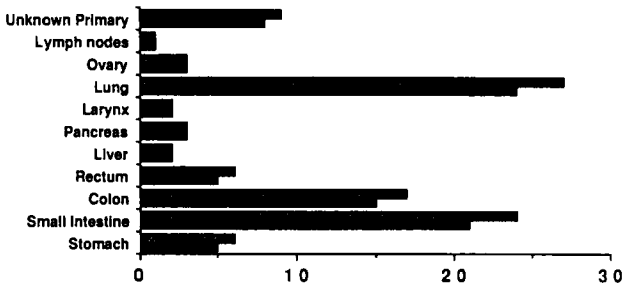

Fig. 1. Distribution of carcinoid tumors. ■=%; ■=No. of cases.

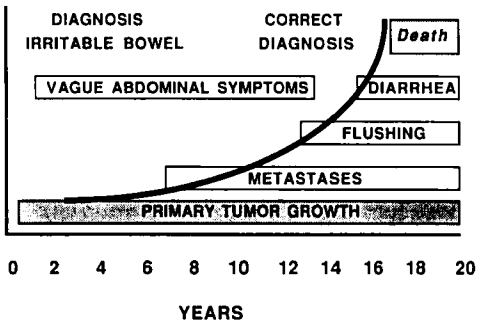

Fig. 2. The natural history of carcinoid.

Table 1

Anatomic distribution of carcinoid tumors (%)

Tumor site	Surg/Clin (6965 cases)	Autopsy (201 cases)
Stomach	2.8	2.5
Duodenum	2.9	0.0
Jejunoileum	25.5	75.6
Appendix	36.2	3.5
Colon	6.0	6.5
Rectum	16.4	1.5
Bronchus	9.9	9.0
Ovary	0.5	0.0
Miscellaneous	0.2	0.0
Unknown primary	3.3	1.0

The age distribution of carcinoids includes patients as young as 10 years of age and people in their ninth decade. The distribution is guassian in nature and the peak incidence occurs in the sixth and seventh decade.

The natural history of carcinoid tumor growth and the resultant symptom complex is illustrated in Fig. 2.

The tumors are slow growing and may be present for years without overt symptoms, and thus escape attention. In the early stages, vague abdominal pain goes undiag-

Table 2

Classification of carcinoid tumors

	Foregut	Midgut	Hindgut
Localization	Stomach, duodenum, pancreas bronchial tree	Jejunum, ileum Meckel's diverticulum, appendix, ascending colon	Transverse, descending, and sigmoid colon, rectum
Silver affinity	Argyrophil	Argentaffin	Nonreactive
Secretion products	5-H Tryptophan, histamine, multiple peptides	Serotonin, bradykinin ?, Prostaglandins ?, Substance P?	?
Functional manifestations	Atypical carcinoid, Zollinger-Ellison, acromegaly, Cushing's, other	Carcinoid syndrome	*Silent

nosed and is invariably ascribed to 'irritable bowel or spastic colon'. Fully, 1/3 of patients with carcinoid tumors present with years of intermittent abdominal pain. Carcinoid tumors can present in a variety of ways. For example, duodenal tumors are known to produce gastrin and may present with the Zollinger-Ellison syndrome. Small, multiple gastric carcinoids are associated with atrophic gastritis, pernicious anemia and chronic thyroiditis. It seems that the loss of the inhibitory influence of gastric acid upon the G cell permits proliferation of both the G and the ECL cells with the ultimate development of carcinoid tumors (6). Patients with carcinoid tumors of the thymus most often manifest hyperparathyroidism or ectopic Cushing's syndrome and bronchial carcinoids are associated with Multiple Endocrine Neoplasia type I. In fact, in a female who has multiple endocrine neoplasia with clinical features of carcinoid syndrome, one should very carefully exclude bronchial carcinoid, whereas in a male with the same clinical syndrome the thymus is the likely site of the tumor.

The major clinical manifestations of carcinoid tumors include cutaneous flushing, which occurs in 84%, GI hypermotility with diarrhea in 79%, heart disease in 37%, bronchial constriction in 17% and myopathy in 7% with an abnormal increase in skin pigmentation in 5% of cases (3). When coexistence of the major symptoms of flushing and diarrhea are sought, it emerges that flushing and diarrhea occur simultaneously in 58%, diarrhea without flushing in 15%, flushing without diarrhea in 5% and 22% of individuals have neither flushing nor diarrhea as a symptom complex.

With metastases to the liver, the correct diagnosis is generally arrived at with a latency, however, of many years. Even then, mistaken identity is not uncommon and unless biopsy material is examined for the neuronal glycolytic enzyme, neurone specific enolase, or the secretory peptide, chromogranin (7) tumors may be erroneously labelled as adenocarcinomas with a negative impact upon survival and attitudes to management.

Diagnosis

Biochemical. The rate limiting step in carcinoid tumors, serotonin, is the conversion of tryptophan into 5-HTP catalyzed by the enzyme in the synthesis of tryptophan hydroxolase. 5-HTP is rapidly converted into 5-HT by another enzyme, the aromatic aminoacid decarboxylase (dopa-decarboxylase). 5-HT is either stored in the neurosecretory granules or may be secreted directly into the vascular compartment. Most of the secreted 5-HT is taken up by platelets and stored in their secretory granules. The rest remains free in the plasma and circulating 5-HT is then largely converted into the urinary metabolite 5-HIAA by the enzyme monoamine oxidase (MAO) and by aldehyde dehydrogenase (AD). These enzymes are abundant in the kidney and the urine typically contains large amounts of 5-HIAA.

In patients with foregut tumors, the urine contains relatively little 5-HIAA but large amounts of 5-HTP and 5-HT. It is presumed that these tumors are deficient in dopa-decarboxylase which therefore impairs conversion of 5-HTP into 5-HT leading to 5-HTP secretion into the vascular compartment. Some is, however, converted into 5-HT and 5-HIAA and thus, the modest increase in these metabolites. The failure of the tumor to convent 5-HTP into 5-HT may account for the increase in urinary 5-HTP with only modest increase in 5-HIAA. The normal range for 5-HIAA secretion is 2–8 mg/24 h and quantitation of 5-HT and all its metabolites is usually capable of detecting 84% of patients with carcinoid tumors. Serotonin enriched food, such as bananas, plantains, pineapples, kiwi fruits, walnuts, hickory nuts, pecans and avocados, and the analgesic acetaminophen, and cough syrups containing quaifenesin may artificially increase 5-HIAA but these sources of errors are not critical in carcinoids with values clearly separated from normal. On the other hand, false negatives may be obtained in patients taking salicylates or l-Dopa. No single measurement detects all cases of carcinoid syndrome, although the urine 5-HIAA appears to be the best screening procedure. Other peptides involved

include substance P, neuropeptide K, pancreatic polypeptide and chromogranin A. In carcinoid tumors, neurotensin is elevated in 43%, substance P in 32%, motilin in 14%, somatostatin in 5% of cases and VIP rarely. In miscellaneous illnesses there may be elevation of these hormones, neurotensin, substance P and motilin 35 and 7% respectively, and up to one-third of people with idiopathic flushing without carcinoid syndrome have elevated levels of a number of neuropeptides (8). We have, furthermore, examined the relationship between the products of the preprotachykinin gene, substance P and neurokinin A in healthy subjects and in patients with carcinoid tumors. Substance P was elevated 80% of the time in patients with carcinoid tumors, whereas neurokinin A was raised in all patients. Why there is a discrepancy in these two peptides, derivating from a common precursor, remains to be resolved.

Localization. A number of techniques have been used to identify the primary site of the tumor and to evaluate the extent of the disease and the presence of metastases. A chest radiogram or CT will suffice to detect a bronchial carcinoid. In contrast, carcinoids of the cecum and colon, or hindgut carcinoids, are usually demonstrable by barium enema examination. The greatest problem derives from small bowel carcinoids which may be small and those in extra intestinal sites. These tumors are usually not identified by upper and lower GI series. Abdominal CT and ultrasound are usually not helpful because the tumors are below the resolution capacity of even the most sophisticated scanning apparatus but, superior mesenteric angiography may be of help. Magnetic resonance imaging has not offered a great advantage over computed tomography. The most recent means of identification of tumors is the use of ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy. At the University of Michigan, this radiolabelled cathecholamine analogue has been used to visualize pheochromocytomas (9, 10). Cells of these tumors are believed to concentrate the imaging agent by a sodium-dependant neuronal pump uptake mechanism. MIBG is, however, also concentrated in platelets and by carcinoid tumors. Our experience is that the technique is only rarely successful but this contrasts with the experience of Feldman et al. (11) at Duke who were able to successfully visualize 10 of 40 patients whose disease had originated in the midgut derived tumors of the ileum or cecum and not those originating from the foregut structures, bronchus, stomach or pancreas. It must be noted that in all instances these tumors were metastases, not the primary tumor.

The standard techniques for determining the presence of hepatic metastases are ultrasound and CT scans of the abdomen and ^{99}Tc^{m} liver spleen scans. The liver spleen scan may be more useful than the abdominal CT. Similarly, bone metastases may be visualized by this technique as well.

In the remaining cases where the tumor has not been identified, we resort to total body venous sampling with measurement of a peptide hormone that is produced. Measurements of 5-HT may be misleading and those of substance P may well direct attention to the source of overproduction of the peptide. This has proved particularly useful in substance P producing tumors (12).

Carcinoid syndrome

Carcinoid syndrome occurs in less than 10% of patients with carcinoid tumors. The principle features of carcinoid syndrome include flushing, sweating, wheezing, diarrhea, abdominal pain, cardiac fibrosis and pellagra dermatosis. Diarrhea is found in 83% of cases, flushing in 49%, dyspnea in 20% and bronchospasm in 6% (13). The relationship between diarrhea and flushing is variable. One can occur without the other and there may be no temporal relationship between the two. The specific etiologic agent(s) for each of the protean manifestations of the carcinoid tumors are not known. Serotonin (14, 15), prostaglandins (16), 5-hydroxytryptophan (17–19), substance P (12, 20), kallikrein (21), histamine (22), dopamine (23) and neuropeptide K (24) are thought to be involved in the clinical manifestations of carcinoid tumors. In addition, symptoms may be related to overproduction of peptides of the pro-opiomelanocortin family, beta endorphin and enkephalin. Pancreatic polypeptide and motilin levels are often raised (25), which may be an important marker of tumor activity and provide a means of monitoring tumor growth and response to therapy rather than contributing to specific symptomatology.

Feldman & O'Dorisio (26) examined the proportion of 43 patients with carcinoid with increased levels of serotonin and various other vasoactive peptides (27). Serotonin, measured either as its urinary excretion, urinary 5-HIAA (28), or whole blood 5-HT (29–31), was raised in 84% of patients with carcinoid tumors and was within normal limits in patients with other tumors and miscellaneous illnesses. Urinary 5-HIAA alone had a 73% sensitivity and 100% specificity. Seven of their patients had normal urinary 5-HIAA levels, but elevated other indices of 5-HT production. Neurotensin and substance P were raised in 43 and 32% of patients and had specificity values of 60 and 85% respectively. False positives occurred in 23 and 26% of patients with conditions other than carcinoid. Motilin and somatostatin were raised in 14 and 50% respectively. These humors may, however, have a better relationship etiologically with the flushing than 5-HT. We have reported a patient who experienced a flushing episode while hormone levels were being monitored continuously. The flushing episode was preceded by a rise in substance P and followed by a rise in serotonin and a fall in histamine levels in blood. Whether this proves to be universal remains to be seen (32). Of note was the finding of a rise in circulating levels of substance P that preceded the flush, whereas 5-HT and histamine levels remained unchanged or fell.

Table 3

Causes of secretory diarrhea

WDHHA syndrome
ZE syndrome
Carcinoid type syndrome
Medullary carcinoma of thyroid
Secreting villous adenoma of rectum
Surreptitious laxative ingestion
Idiopathic

Even though these humors may not prove to be involved in the flushing or diarrhea, they may prove useful as an aid in the localization of ostensibly occult carcinoid tumors. We have previously reported on a patient with a 10-year history of flushing initially precipitated by alcohol ingestion and 4 years' of watery diarrhea (12). Whole body venous sampling with measurements of plasma 5-HT erroneously localized the tumor to the neck for which a negative exploration was carried out. However, substance P levels correctly localized the tumor to the ovary and excision was followed by cure. The false localization was presumably due to 5-HT binding to platelets rendering it difficult to identify gradients in plasma in relation to tumor overproduction.

Diarrhea

The diarrhea syndrome which occurs with carcinoid is usually of a secretory nature. This is best documented either initially by history in which the patient volunteers that the diarrhea persists with fasting or that the diarrhea fails to diasappear when feeding has been curtailed and sustenance is given by the intravenous route. Once it has been establishing that the diarrhea is secretory in nature, the differential diagnosis becomes limited as shown in Table 3.

A history of improvement in the diarrhea with the administration of H_2 receptor antagonists is strongly suggestive of Zollinger-Ellison syndrome. Hypocalemia is frequent with VIP secreting tumors and steatorrhea for all intents and purposes occurs only with the ZE syndrome. Marked metabolic acidosis with bicarbonate wasting is usually only a characteristic of VIP secreting tumors. The villous adenoma of the rectum is notoriously rare and although appearing in many texts, most physicians have yet to see a case. A disturbing cause which may be very difficult to differentiate is laxative abuse and in all circumstances a KOH to detect laxatives is mandatory. Measurement of intestinal secretion by passing a multilumen tube and quantitating electrolytes, and water transport in addition to the measurement of stool electrolytes which should account for the total osmolarity, will help to exclude laxative abuse.

Flushing

Flushing in carcinoid syndrome is of two varieties. With midgut carcinoid the flush is usually of a faint pink to red color and involves the face and upper trunk as far as the nipple line. The flush is initially provoked by alcohol, food containing tyramines such as blue cheese, cake, chocolates, red sausages and red wines. With time the flush may occur spontaneously without provocation. It is usually ephemeral, lasting only a few minutes, may occur many times per day but does not usually leave permanent discoloration. In contrast, the flush of foregut tumors is often more intense, of protracted duration, lasting hours, purplish in hue, is frequently followed by telangiectasia and involves not only the upper trunk but also the limbs. The limbs may become acrocyanotic and the nose resembles that of rhinophyma. The skin of the face often thickens with the appearance of a leonine facies resembling that seen in leprosy and acromegaly.

Flushing cannot always be attributed to carcinoid syndrome. The differential diagnosis of flushing includes: the postmenopausal state, simultaneous ingestion of chlorpropamide and alcohol, panic attacks, medullary carcinoma of the thyroid, autonomic epilepsy, autonomic neuropathy and mastocytosis (Table 4).

The constellation of symptoms of flushing, diarrhea, and cardiac valvular disease, referred to as the 'carcinoid syndrome', occurs in less than 10% of patients with carcinoid tumors. It is more common to see forme fruste presentations of carcinoid tumors. Symptoms have been ascribed to prostaglandins, kinins, and serotonin (5-HT). With the advent of sophisticated radioimmunoassay methods and region specific antisera, a number of neurohumors are now thought to be secreted by carcinoid tumors, including: 5-HT (14), dopamine (23), histamine and 5-HIAA (22), kallikrein (18), SP (17), neurotensin (26), motilin (12, 26), SRIF (26), VIP (33), prostaglandins (16), neuropeptide K (24) and gastrin-releasing peptide (GRP) (26) (Table 5)

Serotonin has long been considered the primary secretory product of most carcinoid tumors, and measurement of 5-HT overproduction, when compared to concentrations of their secretory products, has been reported to have both the highest sensitivity and specificity for carcinoid tumors (26). Our data suggest that 5-HT may have the greatest sensitivity (87%), but may lack specificity, since it was elevated in one of 11 non carcinoid cases. Serotonin, however, may not be the prime mediator of flushing, as we (32) and others (34) have correctly predicted the recurrence of a tumor on the basis of elevated levels of other peptides when urinary 5-HIAA and serum 5-HT values were normal. Therefore, measurement of other peptides may prove useful in monitoring the progress or response to treatment in patients with flushing.

Feldman & O'Dorisio (26) have previously reported the incidence of elevated levels of plasma concentrations of

Table 4

Flushing syndromes	Associated features
Carcinoid-like syndrome	Diarrhea, wheezing, myopathy
Medullary carcinoma thyroid	Mass in neck F.H.
Pheochromocytoma	Paroxysmal hypertension, tachycardia
Diabetes–chlorpropamide/alcohol and autonomic neuropathy	–
Menopause	–
Diencephalic seizures (autonomic epilepsy)	–
Panic attacks	Phobias, anxiety
Mastocytosis	Dyspepsia, ulcer disease, dermatographia
Idiopathic	

Table 5

Secretory products of neuroendocrine tumors

	Peptides	Amines	Other
ACTH	Kallikrein	Dopamine	Prostaglandins
Calcitonin	Growth hormone	Serotonin	
Motilin	Substance P	5-HTP	
VIP	MSH	Histamine	
PTH	ADH	Kinins	
Neurotensin	Neuropeptide K		
Enteroglucagon	Glucagon		
Insulin	Gastrin		
HOG	Pancreatic polypeptide		

neuropeptides (neurotensin-NT, SP, motilin, SRIF, VIP and GRP), and of serum 5-HT concentrations in patients with carcinoid tumors, other tumors, and miscellaneous illnesses. Eighty-four percent of their series had increased 5-HT production, whereas 43, 32, 14, 5 and 0% had elevated concentrations of NT, SP, motilin, SRIF and VIP respectively (26). In spite of the elevated basal concentrations of SP and NT, they were unable to document further increases in these neuropeptides during ethanol-induced facial flushing. While in patients with other tumors or miscellaneous illnesses there was no evidence of increased 5-HT production, there were elevations in the other neuropeptides in as many as 35% of these. Feldman & O'Dorisio concluded that, although measurements of neuropeptides may be helpful in patients with carcinoid tumors, measurements of serotonin overproduction were of more value (26). We do not support this contention and hasten to add that neuropeptide abnormalities occur frequently in patients with flushing.

Several new peptide markers and provocative tests have been developed for diagnosis, localization and follow-up of patients with carcinoid syndrome and liver metastases. Ahlman et al. recently reported the results of pentagastrin (PG) provocation in 16 patients with midgut carcinoids and hepatic metastases (35). All patients tested had elevated urinary 5-HIAA levels and 12 had profuse diarrhea requiring medication. PG uniformly induced facial flushing and gastrointestinal symptoms in patients with liver metastases but had no effect in healthy, control patients. All patients with PG-induced GI symptoms demonstrated elevated 5-HT levels in peripheral blood. Administration of a 5-HT receptor antagonist had no effect on 5-HT release but completely aborted GI symptoms. The authors emphasized the improved reliability of PG compared to calcium infusion, another provocative test popularized by Kaplan et al. (36) and pointed out that PG provocation can occasionally be falsely negative in patients with subclinical disease. Our own experience is that PG induced flushing in 3 patients with gastric carcinoid tumors associated with a rise in circulating levels of substance P (6).

Substance P (SP) has been found in tumor extracts and plasma from patients with carcinoid tumors and in one reported case was useful for tumor localization (12). SP along with neurokinin A (NKA) and its amino-terminally extended form, neuropeptide K (NPK), comprise a group of peptides (tachykinins) with common biological properties (37, 38). Norheim et al. (38) measured peptide responses to PG or ingestion of food or alcohol in 16 patients with metastatic carcinoids and demonstrated 2-fold or greater increases in NKA and NPK in 75% of patients and variable increases in SP in approximately 20% of patients.

Conlon et al. (37) used region specific antisera to SP and NKA to measure circulating tachykinins during a meal-induced flush in 10 patients with metastatic carci-

noid tumors. Five patients had undetectable levels of NKA and SP after stimulation, suggesting that elevated tachykinin concentrations are not a constant feature of carcinoid patients. The authors also studied the effect of a somatostatin analogue administration on meal-induced tachykinin responses in three carcinoid patients. Flushing was aborted in 2 patients but tachykinin levels were only partially suppressed indicating that these peptides cannot be solely responsible for the carcinoid flush.

The observation that tumor markers, such as 5-HT, substance P and the tachykinins NKA and NPK are not universally elevated in patients with metastatic carcinoid should not be surprising. Many other biologically active substances have been implicated in this syndrome including kallikrein, prostaglandins, and histamine just to name a few. The majority of investigations into tumor markers and provocative tests has been conducted in patients with midgut carcinoids and carcinoid syndrome. Since there is no information available from similar studies in patients with gastric (foregut) carcinoids, we cannot even speculate about the possible value of such tumor markers.

Postmenopausal flushing. Approximately 20% of menopausal women seek help for these sudden, repetitive, and often disruptive symptoms, which usually last 1–2 years and then gradually subside. These flushes, visible in 50% of women, may appear as a blush or a patchy flushing of the chest, breasts, neck and face. They generally last 3–5 min, can occur as many as twenty times per day, and may be provoked by warmth, hot drinks, alcohol, and mental stress. Although menopausal flushing resembles that of carcinoid, it is distinguished from that of our patients by the natural history, the generally short-lived response, the lack of a fall in blood pressure, and the absence of upper body telangiectasia. While various hormones (39), catecholamine estrogens (39, 40) and altered adrenergic secretions (39, 41, 42) have been implicated in the cause of menopausal flushing, other neuropeptides have not been studied.

Chlorpropamide alcohol flush. When lightheadedness and/or hypoglycemia accompanies the symptom of flushing, chlorpropamide alcohol flush should be considered. The association among sulfonylurea agents (most often chlorpropamide), alcohol, and flushing has been well described and is commonly referred to as the chlorpropamide alcohol flush, or CPAF. Chlorpropamide appears to affect the intermediate metabolism of alcohol after ethanol is converted into acetaldehyde; it is postulated that the breakdown of 5-HT to 5-HIAA is inhibited and consequent 5-HT accumulation may explain the symptoms of flushing (43, 44). It is estimated that 10–30% of individuals using oral hypoglycemic agents have at least mild symptoms following ingestion of alcohol (45). The flushing generally starts within 3–10 min after drinking alcohol and reaches maximum intensity within 15 min. Episodes usually last about an hour, though they may last longer.

The timing and the duration of the episodes, and the lack of hypotension, syncope, and diarrhea served to distinguish chlorpropamide alcohol flushing from that of carcinoid syndrome.

Panic attacks. Panic attacks are manifested by discrete periods of apprehension or fear and at least 4 of the following symptoms: hot and cold flushes, dyspnea, palpitations, chest pain, choking, paresthesias, feeling of unreality, sweating, faintness, trembling, or fear of dying or doing something uncontrollable during an attack (46). Attacks are estimated to affect 2–5% of the general population (47). They occur predominantly in women (80%), have an onset between the ages of 17 and 30 years and have a chronic fluctuating course (48). Only one of our patients met the definition of a panic attack. Depression among flushing patients is not infrequent, although it may be a consequence rather than a cause of the flushing.

Medullary carcinoma of the thyroid. Facial features or mucosal neuromas often suggest this diagnosis. Protracted flushing of the face and upper extremities, with discoloration and telangiectasia, is a common clinical presentation among patients with MCT, although its special causes remain unknown. The prolonged duration and discoloration of the flush, however, is unlike that seen in patients with midgut carcinoid syndrome but it can mimic that of foregut tumors.

Normal and neoplastic C cells of MCT secrete a variety of biologically active peptides and amines, including calcitonin (49), katacalcin (50), l-dopa (51), ACTH (52), prostaglandins, histamine, substance P, carcinoembryonic antigen (53), and 5-HT (54). Serum levels of 5-HIAA, however, remain normal in problematic cases.

Autonomic epilepsy. Autonomic, or diencephalic epilepsy, is a rare syndrome of paroxysmal autonomic discharges. These patients present with transient episodes of autonomic discharge, including paroxysmal hypertension, tachycardia, and flushing and the diagnosis should be considered in all patients with a history of flushing and unconscious episodes, or other epileptiform behavior. Their adrenergic signs have been attributed to paroxysmal catecholamine release (55).

Diabetic autonomic neuropathy (DAN). Flushing occurs with DAN and is often precipitated by food (gustatatory flush with sweating). The diagnosis can usually be made on the basis of a long history of diabetes mellitus and other symptoms and signs of autonomic dysfunction.

Mastocytosis. This rare and unusual condition should not be mistaken for carcinoid syndrome. The flush is often artificial in nature, with raised macular-papular eruptions of the intervening stain and shows the typical dermatographia. Support for this diagnosis derives from elevated urine or plasma histamine levels as well as increased gastric acid secretion.

Thus, flushing can be caused by a number of disorders, and has been ascribed to a number of substances. Of greatest concern, however, is diagnosing those patients

with carcinoid tumors. Despite their tendency to develop slowly, carcinoid tumors are regarded as malignant neoplasms, and of the known causes of flushing, can be the most harmful. Flushing associated with other disorders can, however, be severe, of longstanding duration, and may be more prevalent than that seen in carcinoid syndrome. Evaluation of the patient with flushing should therefore be directed at excluding the diagnosis of carcinoid. As carcinoid tumors are known to secrete a number of neurohumors (14, 16–18, 22–24, 26, 33), it is necessary to screen for these various peptides if blood 5-HT and/or urinary 5-HIAA levels are normal. Routine imaging procedures, such as CT scans should be performed only if initial urine and/or serum tests are abnormal. If the CT scan reveals abnormal findings, then more specific radiographic evaluation should be considered. Results from more sophisticated procedures, such as MRI may help to define the vascular anatomy of a tumor and MIBG (as in case No. 7) although of potential value in occult carcinoid tumors, has not been evaluated extensively and remains a research tool.

Treatment

Patients with carcinoid may suffer as a result of the endocrine syndrome and/or tumor growth. Surgical removal of the primary tumor is the treatment of choice for small and localized tumors or alleviation of any obstructive symptoms, but surgical cure of carcinoid is almost impossible in the presence of intra-abdominal and hepatic metastases. Different chemotherapeutic agents (56) and surgery or arterial embolization (57) have been used with variable success, but eventual relapse with increasing resistance to the drugs is encountered (58). Since carcinoid is a slow growing tumor, even patients with extensive metastatic disease can enjoy a normal quality of life as long as the endocrine syndrome is quiescent. Different chemical agents, such as methysergide, cyprohepatadine, heparin, phenothiazines, alpha-adrenergic antagonists, corticosteroids, H_1 and H_2 anti-histamine blockers, symptomatic treatment of diarrhea with opioids, and codein have been tried with variable results (58).

Various chemotherapeutic agents, including parachlorophenylalanine, cyproheptadine, methotrimeprazine, corticosteroids, aprotinin, phenoxybenzyamine, and numerous antineoplastic agents have been used in CS with variable success (13, 33). These medications either inhibit serotonin synthesis, act as systemic antagonists of serotonin, or block kallikrein release. Most recently, somatostatin 14 and its long-acting analogue, SMS 201-995, have been used successfully to control symptoms of diarrhea and flushing (59–62) in the carcinoid syndrome. We have had variable experiences with carcinoid syndrome and report below factors which determine responsiveness. A number of individual cases are presented to highlight the heterogeneity of responses.

Since somatostatin has very broad inhibitory effects, somatostatin-14 has been used successfully to suppress diarrhea and flushing in patients with carcinoid tumors (59), but its clinical use is limited by its short half-life (63) with the resulting need for continuous intravenous infusion. With the advent of the long-acting somatostatin analogue (SMS 201-995) (64), it has been used in the treatment of different neuroendocrine tumors including carcinoid.

We have evaluated the effects of SMS 201-995 on clinical, biochemical and tumor growth in 14 patients with histologically proven carcinoid tumors. There were 8 males and 6 females with a mean age of 60 (range 46–80 years). The time interval from diagnosis to initiation of SMS therapy ranged from 2 to 96 months when some patients underwent surgery and/or chemotherapy. Of 14 patients, 12 had diarrhea, 8 had flushing, 3 wheezing, one had tricuspid thickening and insufficiency, 6 had telangiectasia and 3 had a dermatosis. In addition to carcinoid symptoms, 7 of the patients had abdominal pain, 9 weight loss and one had severe proximal muscle weakness. All patients except one had evidence of liver metastases on CT scan.

The primary site of the tumor was in the ileum in 8 patients, 2 in the pancreas and in 4 it was not identified. In spite of laparotomy, due to extensive intra-abdominal metastases, the primary site was not detected in one case, and suspected to be in the pancreas in another case. Two cases did not have a laparotomy and the diagnosis was made by liver biopsy.

Ten patients had resection of their primary tumors and debulking of metastases and 5 patients had chemotherapy.

SMS 201-995 (Sandoz,East Hanover, NJ) was started in an initial dosage of 100 μg subcutaneously every 12 h and the dose was gradually increased to control symptoms and correct paraclinical abnormalities. The maximum maintenance dose that we used was 375 μg every 6 h.

After discharge from the hospital, patients kept a diary regarding the frequency and consistency (formed, soft of watery) of their bowel movements and also episodes of flushing which were graded for duration, extent and severity: 1) face only, 2) face and upper extremities, 3) face and upper extremities and a rise in pulse rate and/or decrease in blood pressure, 4) whole body and a decrease in blood pressure.

The patients were followed in the outpatient clinic with regular physical examinations, total blood count, serum electrolytes, renal and liver functions and measurement of GI hormones and total blood serotonin every 6 weeks. Twenty-four-hour urines for 5-HIAA, CT of abdomen and pulmonary function tests in those with wheezing were repeated every 3 months.

The patients received supplements of pancreatic enzymes whenever steatorrhea was present either before SMS therapy or if changes in bowel habit developed suggestive of malabsorption after SMS therapy. SMS was

Table 6

Clinical and biochemical responses to sandostatin in 14 patients with carcinoid syndrome

	Diarrhea	Flushing	Wheezing	Urinary 5-HIAA	Blood serotonin
Responsives	7 (58%)	8 (89%)	2 (67)	5 (63%)	0
Partial responsives	2 (17%)	1 (11%)	1 (33%)	1 (12%)	1 (10%)
Non responsives	3 (25%)	0	0	2 (25%)	8 (80%)
Worsening	0	0	0	0	1 (10%)
No. of patients (% of total patients)	12 (86%)	9 (64%)	3 (22%)	8 (57%)	10 (90%)

continued as long as the patients wished to receive treatment and had evidence of clinical or biochemical improvement. Patients who showed no response after 6 months of treatment were referred for consideration of chemotherapy. The data are derived from a follow-up of 18–36 months.

The clinical and biochemical responses of all cases are shown in Table 6. The responses to therapy were divided into 4 groups. 1) Responders were: those with more than 75% improvemnet, i.e. a 75% drop in the frequency or intensity of a symptom or 75% drop in the level of a biochemical marker. 2) Partial responders were: those with 25 to 75% improvement. 3) Non responsers were: those with less than 25% improvement and 4) worsening: was judged to occur if the clinical and/or biochemical values increased by more than 25% of their initial estimation.

Our patients were a heterogenous group with advanced carcinoid tumors refractory to conventional chemotherapeutic agents, who were tried on the somatostatin analogue with variable clinical and biochemical responses. We have previously shown a dramatic response of flushing as a symptom to treatment with somatostatin (61). Frohlich et al. (65) have also reported on the value of native somatostatin given by continuous infusion as a means of reversing the PG-induced flushing in carcinoid patients. We, however, were unable to show that PG was a reliable means whereby flushing could be provoked in our patients. Kvols et al. (66) found that 19 of 24 patients with carcinoid tumors had a 50% reduction in flushing, 3 a minor response and in 2 patients the drug failed. Richter et al. (67) showed that 6 of 8 patients had improved symptoms. Our more recent experience is that 64% of our patients presented with flushing as their major symptom. In all instances, the symptom complex improved with a clear decrease in the frequency of symptoms with doses of 1–2 μg/kg/day. In no instance was there resistance to the drug, tachyphyllaxis did not occur and withdrawal of the drug, or substitution with distilled water, was always followed by recurrence of the symptom complex. In contrast to another study (67), relapse of flushing did not occur with continued treatment once it was under control. However, in contrast to the reduction in number of episodes, in certain patients the severity decreased only slightly and the duration of each episode was essentially unchanged.

The extreme example of flushing is the carcinoid crisis with a profound fall in blood pressure. It is deemed unwise to submit a patient to anesthesia or operation without premedication with a combination of adrenergic blocker, steroids, thorazine and aspirin. Kvols et al. (60) has presented data on one such patient, who soon after induction of anesthesia, had a fall in blood pressure unresponsive to intravenous fluid, calcium, neosynephrine or epinephrine administration. Within 1 min of 100 μg of SMS 201-995 given intravenously, blood pressure rose and the patient made an uneventful recovery.

Thus, while it is unclear as to the mechanism of action of SMS 201-995 and the factors mediating flushing and vasodilatation, there can be no doubt that SMS 201-995 is a potent antidote to the vasoactive humors participating in the flush and hypotension. The drug may prove to be a useful adjunct in the preparation of patients for operative procedures and as a standby for the management of carcinoid crises.

Diarrhea occurred in 86% of our patients and responded variably to SMS. The acute effect of SMS on water and electrolyte transport in 6 patients with diarrhea is shown in Fig. 3.

The pattern changed from a secretory toward an absorptive state in 5 out of 6 patients. Acute administration of SMS, thus, normalized the water and electrolyte transport across the proximal intestine, as has been shown in patients with WDHHA syndrome (62, 68). The acute reduction in electrolyte secretion did not, however, predict the long-term response of diarrhea to SMS therapy, but this needs to be further examined in a larger number of patients. Only 58% of our patients with diarrhea had complete remission, a finding that differs from the improvement in 19/25 patients reported by Kvols et al. (66). This could be due to the fact that diarrhea in patients with carcinoid tumors has multiple etiologies, i.e. secretory, increased motility, malabsorption, partial luminal lymphatic obstruction, bacterial overgrowth and short bowel syndrome due to surgical resection. The diarrhea may even appear to worsen with the appearance of steatorrhea

and the physician is not infrequently faced with the confounding situation of not knowing to what to attribute the symptom. However, although somatostatin does inhibit exocrine pancreatic secretion (69), addition of pancreatic enzyme supplementation has not uniformly decreased SMS-induced steatorrhea (70). We did not find any consistent changes in frequency or consistency of bowel movements in response to pancreatic supplement in those patients with steatorrhea before treatment or the bowel habits after therapy with SMS 201-995 compatible with the notion that the steatorrhea has a complex pathogenesis and may be contributed to be alterations in bile flow, the direct effects of somatostatin on nutrient absorption and intestinal motility (71).

The significant improvement in water and electrolyte transport across the small intestine after the initial dose of SMS without significant changes in blood serotonin, implies a direct effect of SMS on the target organ independant of serotonin mediation (72). Responses of 2 individual cases are shown in Figs 4–6.

All 3 of our patients with wheezing had clinical improvement and spirometric improvement was documented. Pulmonary function did not improve further after 3 months of treatment indicating an irreversible component of small airway disease secondary to long-standing smoking.

Patient No. 10 in our series presented with severe proximal muscle weakness with normal muscle enzymes and nerve conduction studies, but electromyographic features of a proximal myopathy. Although a neurological deficit secondary to metastatic carcinoid has been seen (73), metabolic induced neuromuscular disease is very rare (74–76). Although our patient had a history of hypokalemia, at the time of admission his potassium was normal with no biochemical evidence of thyrotoxicosis, ectopic ACTH production or, osteomalacia. We believe that his severe myopathy was due to his carcinoid, although it might have been aggravated by severe diarrhea, weight loss and poor nutrition. Histological changes can be induced in skeletal muscle of mice by intraperitoneal injection of 5-HT (77). Three months after SMS therapy, the patient did not have any clinical evidence of myopathy with improvement in electromyographic features.

There are conflicting reports regarding the biochemical responses of carcinoid patients to somatostatin. Richter et al. (67) reported a significant drop in 5-HT in 8 patients treated with 150 μg/day of SMS 201-995, but no changes in urinary 5-HIAA while others have found a drop in urinary 5-HIAA (72). In prolonging their treatment of 4 of their patients to 15–30 weeks, blood 5-HT remained unchanged (70). In our patients, urinary 5-HIAA dropped in almost all patients and normalized in one-third of the patients. Fig. 7 compares the urinary 5-HIAA before SMS therapy with the nadir values after therapy. Four out of 8 patients normalized their 24-h 5-HIAA. In case 8, urinary 5-HIAA initially dropped but subsequently rose. The overall post

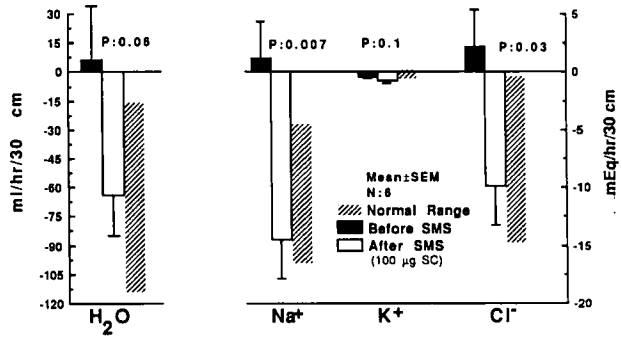

Fig. 3. Intestinal secretion of water and electrolytes. Secretion was measured in a 2 feet segment of jejunum using a multilumen tube and infusion of an electrolyte mixture containing polythylene glycol as a marker for recovery of fluid and electrolytes. The hatched areas indicate normal transport and negative numbers indicate net absorption.

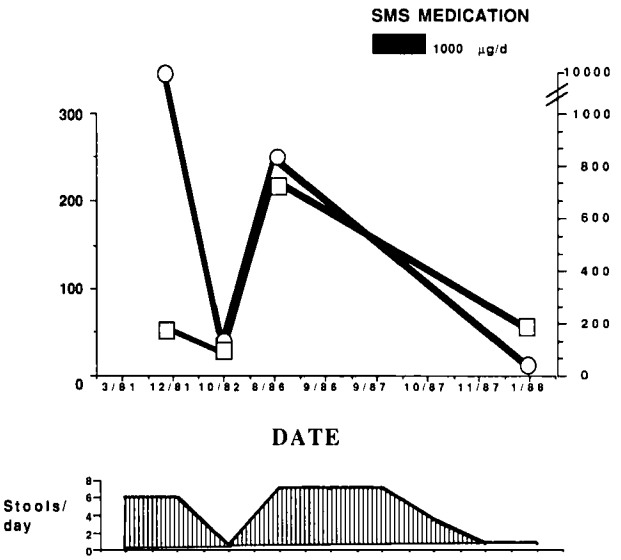

Fig. 4. Patient FH, 68 y. female with metastatic PPoma. A carcinoid tumor which elaborated both VIP and PP. Note resistance to all forms of treatment with the ultimate need for i.v. alimentation and chemotherapy. *March 1981:* watery diarrhea 8–10 stools/d. *Dec. 1981:* secretory diarrhea, hypervascular mass in pancreas, PP >1000 pg/ml, VIP 50 pg/ml. *Oct. 1982:* 80% distal pancreatectomy (mass 7 cm), histochemistry and five PP, TCT, 5-HT. Postop. PP 142 pg/ml. No diarrhea. *May 1986:* Recurrence of secretory diarrhea (9–11 stools/d), multiple liver met. (CT + angio), PP 820, VIP 221. Tumor biopsy, histochemistry positive VIP, PP. Gastrin, chromogranin, NSE. SMS treatment 200 μg (bid). Diarrhea decreased to 2 stools/d. *Sept. 1986–Sept. 1987:* Recurrence of diarrhea, hypokalemia and weight loss. Intrahepatic chemotherapy, hepatic irradiation. *Oct. 1987:* Diarrhea 3–4 l/d. SMS treatment 7800 μg/d and continued SMS s.c. infusion, stellazine, lithium, diagoxin, Ca blockers, indomethacin, meclomen. Continuous diarrhea 1.5–3 l/d. Bleeding from GI tract. *Nov. 1987:* Hickman catheter sepsis. Well-diarrhea 0.5–1 l/d. Weight stable. *Jan. 1988:* Well. Weight stable. Diarrhea 0.5–1 l/d. VIP 56, PP 1288. VIP (□—□; pg/ml), PP (○—○; pg/ml).

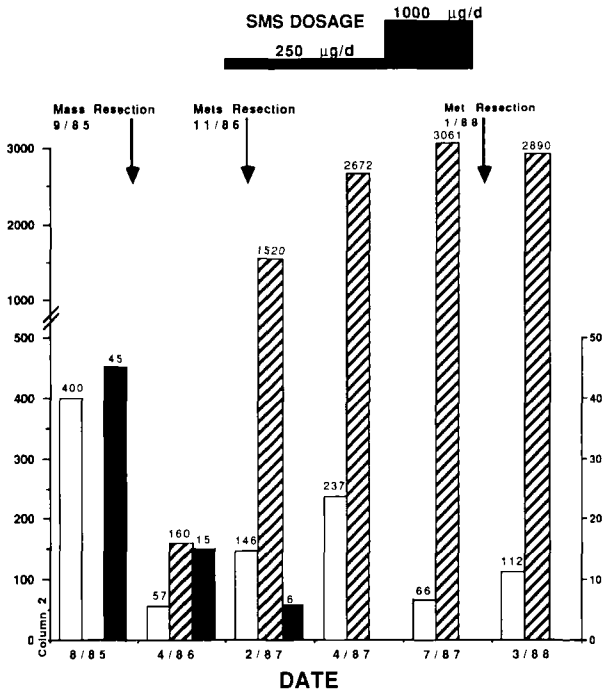

Fig. 5. Patient DK, 33 y. female with metastatic CRFoma. The clinical course of a patient with a metastatic neuroendocrine tumor that secreted ACTH, corticotrophin releasing factor and gastrin. Resection of the primary tumor cured the Cushing's syndrome with return of basal cortisol levels to normal. Despite SMS treatment metastases continued to grow and secrete gastrin. Note that this was only detectable in the early stages using secretin provocative tests for gastrin secretion. *1968–1977:* Dyspepsia, peptic ulcer, bleeding. Treatment with antacids and H2 blockers. *1978:* Pyloroplasty + vagotomy. *1984:* Weight gain, acne, Cushingoid. *1985:* Increased gastrin, ulcers. Positive secretin test. Pancreatic mass (CT). Sept. 1985: Laparatomy with resection of mass. Histochemistry positive gastrin, ACTH, somatostatin, glucagon. *Sept. 1986:* Total resolution of Cushing's. Gastrin increases from 67 to 217. *Nov. 1986:* Met. in left liver lobe (CT). Resection of 3 mets. BAO 4.6, MAO 7.8 meq/h. Secretin test gastrin 145→1667. Cortisol 15→47. ACTH 37, 5-HT 268. SMS treatment is started (100 µg/bid). *April 1987:* Gastrin 240 2910. Continued SMS (250 µg tid). *July 1987:* Gastrin 66→3107. Met. right liver lobe. Continued SMS (250 µg qid). *Dec. 1987:* Met. has increased in size. 5-HT 181, subst P 92. Resection of liver met. *March–Nov. 1988:* Gastrin 115→2890. Cortisol 17→7.5 SMS discontinued. Secretin-stimulated gastrin (■; pg/ml), basal gastrin (□; pg/ml), cortisol (■; pg/ml).

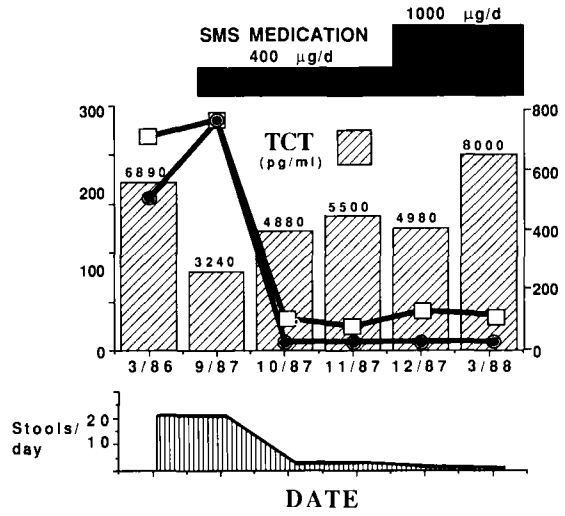

Fig. 6. Patient CL. Metastatic calcitoninoma. The clinical course of a patient with extensive liver metastases. Note the dramatic reduction in diarrhea, PP and VIP levels but unresponsiveness of calcitonin. *1986:* Diabetes 20 years, insulin requiring. Intermittent diarrhea 15–20 stools/d. K acidosis. *Aug. 1987:* Weight loss 30 lb. Mass in left adrenal and enlarged pancreas body (CT). *Nov. 1987:* Mets in very large liver. Gastrin 117 pg/ml, PP 512 pg/ml, TCT 6890, VIP 269 pg/ml Biopsy showed neuroendocrine carcinoma. Pos. chromogranin NSE/liver + 5-HT, TCT, NSE, VIP, Adr. Venous sampling shows increased TCT and VIP, left adrenal vein. SMS treatment started, 150 µg every 6 h. VIP (□—□; pg/ml), PP (⊖; pg/ml).

SMS 24-h urinary 5-HIAA was significantly lower than the basal values ($p<0.05$).

The blood serotonin levels during the course of therapy are shown in Fig. 8. Although few of our patients had a fall in their blood serotonin level, the overall post-SMS values were not significantly lower than pretreatment values.

There was no clinical correlation between clinical responses and either the urinary 5-HIAA or the blood serotonin level. For contrast, in patients in whom the urinary 5-HIAA fell there was clinical improvement in one or more of the symptoms. This may reflect the fact that there are multiple etiologic factors involved in the symptomology of carcinoid tumors. In our patients, those who responded clinically required no more than 500 µg/day to control their symptoms, although we have examined the response to higher doses in certain instances.

Due to the slow growth of carcinoid tumors, it is difficult to assess the effect of SMS on the rate of tumor growth or regression. Shrinkage of liver metastases in patients with carcinoids (62, 66) and other functioning pancreatic neuroendocrine tumors (78) has been reported. We have had variable experiences. Patient VW was seen in 1980 with watery diarrhea 2–3 times per day, vomiting after meals and weighed 140 lb. A diagnosis of spastic colon was made. In May 1984, CT showed an enlarged liver which was shown to be an adenocarcinoma on biopsy in January 1985, for which she received 4 months of chemotherapy with 5-fluorouracil. After 4 months she perforated a gastric ulcer and laparotomy biopsy revealed a metastatic carcinoid tumor. VIP levels post-operatively were found to be in the >1000 pg/ml region (normal<150 pg/ml). In September 1985, she was seen at the University of Michigan and was found to have almost complete replacement of the right lobe of the liver with metastases and had lost 45 lb weight. Initiation of SMS treatment resulted in cessation of diarrhea and 6 months later she

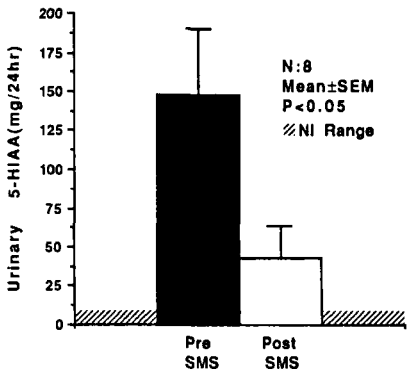

Fig. 7. Urinary 5-HIAA responses to SMS in patients with carcinoid tumors.

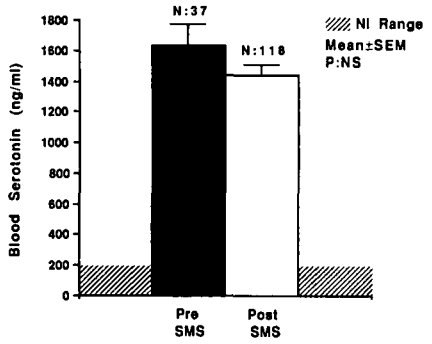

Fig. 8. Blood serotonin responses to SMS in patients with carcinoid tumors.

presented with severe right upper quadrant pain and CT showed infarction of the tumor and VIP levels had returned to the near normal range. The clinical course and VIP levels are shown in Fig. 9.

The relationship between tumor size and growth and the biochemistry is not a simple one. In one patient the tumor clearly shrank, but ACTH levels rose to the 2000–3000 pg/ml range. On molecular sieve chromatogrpahy, the ACTH coeluted with native ACTH, but the patient has no clinical features of Cushing's, is gaining weight and has no diarrhea or flushing. Another patient had progression of tumor growth after 18 months of SMS therapy, yet there was a dramatic fall in blood serotonin values and the patient is entirely asymptomatic. The opposite is also not unusual, wherein there is no change in tumor size, a very well patient and hormonal levels that are unaffected by SMS even in doses as high as 1000 μg/day (75).

We have follow-up CT in 14 patients. Two showed some regression of the tumor, and in one case it infarcted. Five cases showed progression and 7 cases showed no changes on the CT scan followed for up to 2–5 years. Currently, we are using higher doses of SMS to see if we can suppress all biochemical markers and also tumor growth.

No major clinical side effects have been observed in our patients. Initially, during injection of somatostatin a few patients experienced a burning sensation at the site of injection that improved with slow injection of the drug. A few patients had nausea and/or light headedness immediately after injection, lasting up to 30 min, that gradually faded with repeated injection. We have also had 3 patients present with acute calculous cholecystitis after 18 months to 2 years treatment with SMS, but retrospective analysis revealed the presence of gallstones on CT done before the advent of SMS treatment. We have also observed that steatorrhea seems to occur in a dose-dependant manner. With doses greater than 500 μg/day, steatorrhea is almost universal, but as mentioned above, does in some instances respond to pancreatic enzyme supplements.

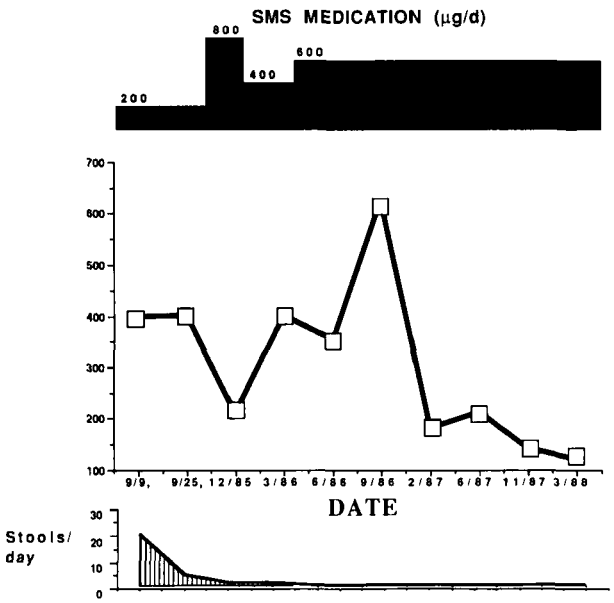

Fig. 9. Patient VW. Clinical course of a patient with metastatic vipoma with a dramatic reduction in VIP and spontaneous infarction of the hepatic metastases after treatment with SMS. VIP (□—□; pg/ml).

Conclusion. Short of an effective curative or palliative agent, SMS can control flushing and wheezing in most and diarrhea in some patients with carcinoid tumors with improvement of their general condition. The effects of SMS on tumor growth needs to be further evaluated in relation to the slow progression and indolent nature of these tumors. Since little effective therapy is available and much may be harmful, it seems not unreasonable to offer SMS 201-995 for the control of symptoms and for palliation at this point in time. Limits of safe and effective dosage need to be established and long-term follow-up is a prerequisite to defining the ultimate role of this form of peptide therapy in the carcinoid syndrome..

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