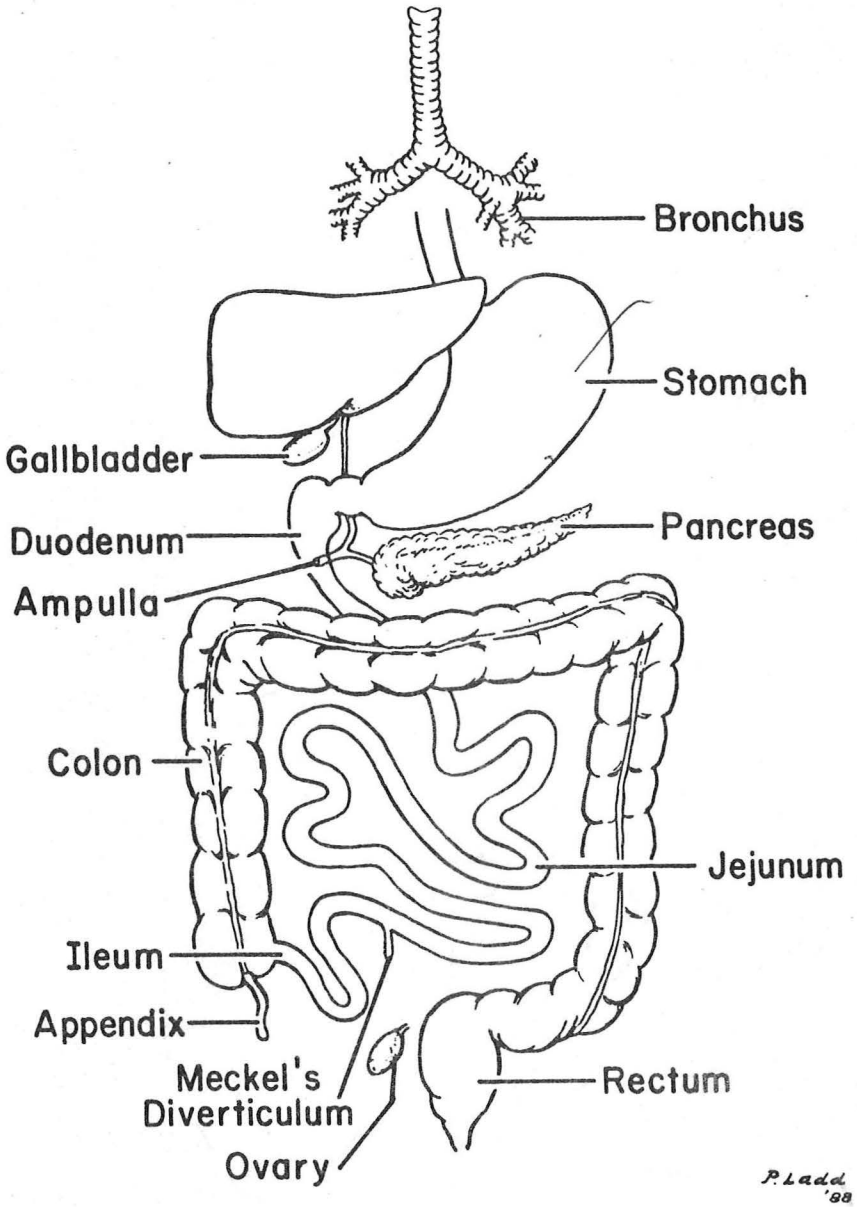
INTERNAL MEDICINE GRAND ROUNDS

"CARCINOIDS AND THE CARCINOID SYNDROME"



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INTRODUCTION

L.H. 56 y/o man, with carcinoid syndrome

1979 - Shortness of breath, weakness, flushing, telangiectasia, diarrhea and intolerance to wine

11/82 - Hospitalized at DVAMC; a diagnosis of carcinoid syndrome was made on basis of symptoms and a 5-hydroxyindoleacetic acid level (5-HIAA) of 297 mg/24 h (normal 2.1-8.7 mg/24 h).

Liver scan - large focal defect in superior aspect of right hepatic lobe; multiple focal defects throughout liver.

Spleen - focal defects

Liver biopsy - carcinoid

Therapy - Periactin and niacin

10/83 - Flushing and diarrhea persisted

Cardiac catheterization - severe tricuspid regurgitation with mild tricuspid stenosis.

Transferred to General Clinical Research Center at Parkland where he was treated by Dr. G. Krejs with ketanserin (a 5-hydroxy-tryptamine receptor antagonist).

5/84 - Admitted to DVAMC with ascites, edema of both ankles and legs, severe right ventricular failure and hepatosplenomegaly

Radionuclide Blood Pool Imaging Study - Three to 4+ dilatation of both chambers of right heart; findings consistent with tricuspid regurgitation.

Patient also had pulmonary valve disease

6/84 - Tricuspid valve replacement; pulmonic valve excision

8/85 - Final DVAMC admission

The carcinoid syndrome was first described in June, 1954, in an article entitled "Malignant Carcinoid of the Small Intestine with Metastases to the Liver, Valvular Disease of the Right Side of the Heart (Pulmonary Stenosis and Tricuspid Regurgitation without Septal Defects), Peripheral Vasomotor Symptoms, Bronchoconstriction and an Unusual Type of Cyanosis" (1). Patient L.H. had most if not all of these signs and symptoms. Many carcinoids have the ability to metastasize to the liver and cause the carcinoid syndrome. Some, however, like ovarian carcinoids, can cause the syndrome without metastasis to the liver since their products drain directly into the vena caval circulation. The carcinoid syndrome represents a very interesting array of symptoms including flushing, diarrhea, and abdominal pain along with important diseases such as carcinoid heart disease as illustrated in the case of L.H.

Carcinoids, on the other hand, were described more than a century ago (2) and have provided a continued source of interest and controversy both to the clinician and the pathologist with regard to their classification, pathogenesis, biological behavior and diagnosis (3). Oberndorfer introduced the term *carcinoid* to describe a morphological subset of small sized intestinal neoplasms - *die kleine Carcinome* - which behaved less aggressively than the more common intestinal adenocarcinomas (4). Through the years, carcinoids have been described in other areas of the body other than the intestinal tract such as the lungs and bronchi, larynx, thymus, ear, ovary, prostate and skin.

Electronmicroscopy, histochemistry and immunohistochemistry have contributed new criteria for the diagnosis of carcinoids and have added new dimensions to our comprehension of the biology of these neoplasms (3). As new techniques have evolved, they also have created problems for diagnosis and classification of the tumors. While some pathologists have restricted the term *carcinoid* to those tumors resembling intestinal carcinoids by light microscopy, others have made the diagnosis on the basis of silver reactivity, the demonstration of membrane-bound secretory granules by electron microscopy or by the identification of various hormones by immunohistochemistry.

Many of the concepts of carcinoid tumors have undergone considerable revision and evolution since these neoplasms were first described. Presently, carcinoids are considered to be tumors composed of endocrine cells derived from the primitive gut. Using this definition, tumors of similar morphology may derive not only from the gastrointestinal intramucosal (serotonin containing), endocrine cells or their precursors, but also from an extensive family of extraintestinal endocrine cells. These have the ability to synthesize and store both biogenic amines and a variety of regulatory peptides. The availability of specific antisera directed against these hormonal products along with immunohistochemical techniques are of paramount importance not only in defining the hormonal profiles but also in establishing the origins of many of the neoplasms derived from the diffuse endocrine cell system (3).

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ENDOCRINE CELLS OF THE GASTROINTESTINAL TRACT

Carcinoids are composed primarily of endocrine cells. Many of the endocrine cells contain similar substances whether they are located in the gastrointestinal tract, the bronchial tree, the ovary or some other location, especially since they all are believed to have originated from the primitive gut. This section will describe the history surrounding the discovery of endocrine cells in the normal gastrointestinal tract, some of the substances within these cells and also the techniques used to identify the cells and localize their secretory products.

Heidenhain, in 1870, was the first to report specialized cells in the digestive tract (1). He described small, yellow-brown cells in the mucosal glands of the dog intestine. Through the years these cells have been called by various names including acidophilic cells by Kultschitzky (2), chromaffin cells by Schmidt (3) and enterochromaffin cells by Ciaccio (4). Masson, in 1914, who named the cells, argentaffin cells, based on the fact that the cells incorporated and precipitated silver salts (5) also suggested for the first time that the role of these specialized cells might be endocrine in nature. He also indicated that these cells released substances into the bloodstream which, in turn, caused effects in other parts of the body distant from the intestinal tract. This observation was about 12 years after Bayless and Starling discovered and described the first hormone, secretin (6). It was an extract of duodenal mucosa which, when injected into the bloodstream, stimulated the secretion of water and bicarbonate by the denervated pancreas. The intestinal tract is probably the largest endocrine gland in the body. Since 1902, more than 40 peptides have been characterized, immunolocalized or assumed on the basis of physiological action to be located in the digestive system (7).

Pearse was the first to point out in 1966 that a number of cells throughout the body have in common the major function of amine and/or peptide production and also share several cytochemical features (8,9). These features include the following within the cytoplasm of the cells: 1) fluorogenic amines or their precursors, 2) non-specific esterases and/or cholinesterase, and 3) α-glycerophosphate dehydrogenase.

In 1968, Pearse and his colleagues (10) introduced the term APUD to express the major unifying characteristics of these cells, that is, their capacity for Amine Precursor Uptake and Decarboxylation. The widely distributed endocrine cells of the gastrointestinal tract have this ability and are thought to be part of the APUD cell system, although in the view of some, this concept has fallen into disfavor. Initially, these cells were believed to be derived from the neural crest (11) although other workers have refuted this concept (12,13). Currently, many investigators believe that the endocrine cells in the gastrointestinal tract have an endodermal origin rather than the neural crest as the site of origin as believed originally (7).

Most endocrine glands are formed by hormone-producing cells that are grouped together such as the thyroid, parathyroid and adrenal glands. In contrast, the endocrine cells of the gastrointestinal tract, are scattered throughout the digestive system. Feyrter, in 1938, was the first to recognize this feature and called attention to the diffuse endocrine epithelial organ of the gastrointestinal tract (14). The peptides and bioamines in the human digestive tract, their site of localization and major functions are listed in Table 1.

TABLE 1. PEPTIDES AND BIOAMINES IN THE HUMAN DIGESTIVE TRACT, THEIR SITE OF LOCALIZATION, AND MAJOR FUNCTION (from Ref 7)

SUBSTANCE	LOCALIZATION	MAJOR FUNCTION
Cholecystokinin	I cell of the small intestine	Pancreatic enzyme secretion
Enkephalins	Digestive nerves	Motility inhibition?
Gastric inhibitory peptide	K cell of the small intestine	Stimulus of insulin secretion
Gastrin	Antral G cell and intestinal IG cell	Stimulus of gastric acid secretion
Gastrin-releasing peptide (bombesin)[a]	Digestive nerves	Gastrin release, acid secretion
Glicentin (glucagon-like immunoreactivity)	L cell of the small and large intestine	Glucose regulation?
Histamine	Mast cells	Stimulus of gastric acid secretion
Motilin	M cell of the small intestine	Interdigestive intestinal motility
Neurotensin	N cell of the ileum	Vascular regulation?
Norepinephrine	Extrinsic digestive nerves	Vascular regulation
Pancreatic polypeptide (PP)	PP cell of the small intestine?	Pancreatic enzyme inhibition?
Polypeptide YY	Unknown colonic cell	Unknown?
Secretin	S-cell of the digestive tract	Stimulus of bicarbonate secretion from pancreas
Serotonin	EC cells of the digestive tract	Stimulus of digestive peristalsis
Somatostatin	D cell of the digestive tract	Multiple inhibitor?
Substance P	Digestive nerves, EC, and unknown cells	Neurotransmitter?
Urogastrone (epidermal growth factor)[a]	Undefined duodenal structures	Inhibition of gastric acid
Vasoactive intestinal polypeptide	Intrinsic digestive nerves	Neurotransmitter?

a Analog substances (nondigestive peptide listed in parentheses).

The work of Erspamer (15) and Hamperl (16) led to the first clear indication that endocrine cells of the gut were not a homogeneous group of cells but instead had several identities. These authors coined the term argyrophil to refer to some carcinoid cells that incorporate silver salts. In contrast to the argentaffin cells, which also incorporate silver salts, the argyrophil cells require an exogenous reducing substance to precipitate silver. This indicated that there were at least two types of endocrine cells. One disadvantage to the silver staining techniques is that their specificity is relatively low (7). Silver staining methods are useful, however, for the non-specific diagnosis of most gut endocrine cells and their tumors.

Electron microscopic observations led to the establishment of reliable morphologic criteria for classification of endocrine tumors (7). The initial classifications designated these cells exclusively with letters. In some cases, the cells in the gastrointestinal tract were named after their morphologic counterparts in the pancreatic islets, for example, D cells. In some instances, cells were named at least in part by their functional characteristics (7): EC for enterochromaffin cells or G cells for gastrin-producing cells. Later, letters were assigned to cells based on some morphologic features. Finally, in meetings that took place in 1969, 1973, 1977 and 1980, an unified system of nomenclature for classification of gut endocrine cells was established. Current classifications are based primarily on ultrastructural characteristics of the secretory granules of the various cells.

The next major advance in identifying peptides and amines was the development of immunofluorescence. Gastrin containing cells were the first to be identified but with time, cells containing other peptides such as secretin, cholecystokinin, gastrin-releasing peptide, motilin, vasoactive intestinal peptide, somatostatin and bombesin were localized and characterized (7).

Immunoperoxidase techniques have progressively replaced immunofluorescence methods in the study of endocrine cells of the gut and their tumors. These methods do not require the presence of a fluorescence microscope, as they yield more stable preparations and have increased sensitivity.

Immunocytochemistry has been utilized also to localize marker substances common to most or all endocrine cell types (7). Examples of these markers which are capable of identifying normal as well as neoplastic neuroendocrine cells are substances such as neuron specific enolase (17), chromogranin and synaptophysin (7). Immunocytochemistry has added another dimension to the study of endocrine cells. Whereas previous methods had been based on morphology of the cells, immunocytochemistry added another dimension founded on cell function.

Neuron specific enolase is the name given to the γ-subunit of 2-phospho-D-glycerate hydrolase, because it has been expressed preferentially in neurons and other cells presumed to be of neuroendocrine origin (18). The fact that this enzyme is present in endocrine cells has been interpreted by some to mean that the endocrine cells of the gut originate from the neural crest (13). However, there is considerable controversy as to the neural origin of all cells stained with antibodies against neuron specific enolase. Regardless of the controversy, immunoreactivity to neuron specific enolase is often used to diagnose endocrine cells of the digestive tract and their tumors.

Chromogranin is another marker that has been used to identify endocrine cells of the gastrointestinal tract (19). Chromogranin is associated with

cytoplasmic secretory granules and is detectable only in those cells which store their products in granules. This is in contrast to neuron specific enolase which is a cytosolic protein present in most neuroendocrine cells irrespective of whether they store a neuropeptide in granules.

With the development and evaluation of various technical advances and staining techniques, there has been steady advancement in the knowledge of the structure and function of endocrine cells of the gastrointestinal tract. This also has led to a better understanding of the morphology and neuropeptide content of tumors of endocrine cells, specifically carcinoids in the digestive tract and other parts of the body.

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HISTORY OF CARCINOIDS

The history of carcinoids is summarized in Table 2.

TABLE 2. HISTORY OF CARCINOIDS

DATE	OBSERVATION	REF
1888	Lubarsch described multiple small tumors at autopsy in the distal ileum of two patients	2
1890	Ranson described a patient with ileal carcinoma and multiple liver metastases who experienced diarrhea and dyspnea induced by eating	3
1907	Oberndorfer introduced the term "Karzinoid" to describe a morphologically distinct class of intestinal tumors that behave less aggressively than the more common intestinal adenocarcinomas	4
1914	Gosset and Masson demonstrated that carcinoid tumors might arise from enterochromaffin cells (Kulchitsky's cells) of the glands of Lieberkühn. They used a silver impregnation technique and demonstrated that these cells had an affinity for silver salts (argentaffin cells). They also suggested that these tumors were of endocrine origin as had been proposed previously by Ciaccio(6).	5
1953	Lembeck demonstrated the presence of serotonin in carcinoid tumors	7
1954	Thorson and colleagues first described a series of patients with small intestinal carcinoids and hepatic metastases, establishing the clinical entity of the "carcinoid syndrome"	8

Most carcinoid tumors are clinically silent and therefore are classified according to morphologic and biochemical characteristics rather than clinical features. In general, carcinoid tumors are derived from the diffuse gastrointestinal endocrine system described in the previous section. Endocrine cells occur in all regions of the gastrointestinal tract except the esophagus although an occasional carcinoid has been described in the esophagus, including a mixed adenocarcinoma and carcinoid tumor of the esophagus. In the small intestine, the cells are most frequent in the duodenum, terminal ileum and appendix. In the large intestine, they are more sparsely distributed. They rarely occur in the ascending colon but occur in the descending and sigmoid colon and in the rectum.

Development of immunohistochemical techniques has allowed the identification of sites of synthesis and storage of peptides in cells and nerve fibers of the gastrointestinal tract and the pancreas (1). This has provided recognition of synthesis and secretion of hormonal peptides as well as of biogenic amines by carcinoids. Carcinoid tumors are now considered neoplasms that contain cells which produce either peptides or amines or both and this, in turn, explains the different hormonal profiles of the tumors based on their site of origin (1).

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PEPTIDES AND AMINES OF CARCINOIDS

Cells within carcinoids also contain peptides and synthesize and store serotonin and other biogenic amines. The same or similar techniques used to identify peptides and amines described in the previous section can be used to identify peptides and amines in tumor cells. Studies have been performed using immunohistochemical staining techniques to search for various substances in carcinoids. Results of one extensive review in which 26 carcinoids were stained with a panel of immunohistochemical stains is shown in Table 3 (1). In the 26 cases illustrated in this Table, serotonin was present in 21 of the tumors. None of the tumors contained ACTH or secretin but the other neuroendocrine products tested were present in several of the tumors and some tumors contained more than one peptide. For example, neurotensin was present in five tumors, gastrin in six, somatostatin in five and motilin in three. Even though this was a carefully performed and controlled study, immunohistochemistry can never allow absolute identification of a neuropeptide. Positive-staining should be interpreted as "hormone-like immunoreactivity" rather than an absolute confirmation of a specific hormone within a given tumor.

Neuropeptides have been measured and reported in additional studies. In one experiment, pancreatic polypeptide and glucagon were found in 9 out of 19

TABLE 3. RESULTS OF IMMUNOHISTOCHEMICAL STAINING IN PATIENTS WITH INTESTINAL CARCINOIDS (FROM REF. 1)

CASE	LOCATION OF PRIMARY TUMOR	AGE/SEX	IMMUNOHISTOCHEMICAL FINDINGS								
			SER	ACTH	NEURO	GASTRIN	SOM	MOT	SEC	GLU	PP
1	Jejunum	39/M	-	-	-	+	-	-	-	-	-
2		28/F	+	-	-	-	-	-	-	-	-
3		69/M	+	-	-	-	-	-	-	+	-
4	Ileum	48/M	+	-	-	-	-	-	-	-	-
5		62/M	+	-	-	+	-	-	-	-	-
6		59/M	+	-	-	-	-	-	-	-	-
7		56/F	+	-	-	+	-	-	-	-	-
8		52/M	-	-	-	+	+	-	-	-	-
9		45/M	+	-	-	-	-	-	-	-	-
10		52/F	NT			NT					
11		61/F	NT			NT					
12		66/F	+	-	-	-	-	-	-	-	-
13		62/M	+	-	-	-	-	-	-	-	-
14		56/M	+	-	-	+	-	-	-	-	+
14a*	Appendix	56/M	+	-	-	-	+	-	-	-	+
15		48/F	+	-	-	-	-	-	-	-	-
16		17/F	+	-	-	-	+	+	-	-	+
17		24/M	+	-	+	-	-	-	-	-	-
18		32/M	+	-	+	-	-	-	-	-	-
19		54/F	+	-	-	-	-	-	-	-	-
20		66/M	+	-	-	-	-	-	-	-	-
21		62/M	-	-	+	+	+	+	-	+	-
22		26/F	+	-	-	-	-	-	-	-	-
23	Cecum	72/F	-	-	-	-	-	-	-	-	-
24	Colon	57/M	+	-	-	-	-	-	-	-	-
25	Rectum	35/M	+	-	+	-	-	-	-	+	+
26		63/M	+	-	+	-	+	+	-	+	+

NT: not tested; ser: serotonin; neuro: neurotensin; som: somatosatin; mot: motilin; sec: secretin; Glu: glucagon; PP: pancreatic polypeptide hexapeptide.
* Cases 14 and 14a represent data from two tumors in the same patient.

carcinoids (2). Furthermore, the wall of the intestine contains large amounts of substance P (3) and substance P-like immunoreactivity has been found in nerves as well as endocrine cells in the intestinal tract (4,5). Substance P has been identified in carcinoid tumors and metastases from carcinoid tumors. However, from a quantitative assessment of the number of substance P-containing cells and the total number of endocrine cells in the intestine, many and probably most endocrine cells do not contain substance P (6).

Ten patients with liver metastases from a midgut carcinoid were evaluated in another study (7). Substance P was measured in peripheral blood in 5 patients and from hepatic venous blood in another 5 patients. In each patient, substance P was elevated in both peripheral blood and hepatic venous blood. Substance P also has been measured from the venous drainage from an ovarian carcinoid in a patient with carcinoid syndrome (8).

Rectal carcinoids also contain neuropeptides as illustrated by the results from the two rectal carcinoids illustrated in Table 3. Twenty-five rectal carcinoids were examined immunohistochemically for various peptides in another study (9). Fourteen of the 25 rectal carcinoids contained pancreatic polypeptide and 13 contained glucagon. Other peptides (in decreasing order of presence in the tumors) were somatostatin, insulin, enkephalin, substance P and β-endorphin. In another series of 27 patients, enkephalin and β-endorphin were identified in 2 rectal carcinoids (9,10).

Other neuropeptides also have been found in carcinoids. For example, neurokinin A and neuropeptide K have been isolated from mammalian tissues and have been found in extracts of carcinoid tumors. As will be discussed later, neurokinin A-like immunoreactivity and substance P-immunoreactivity have been found in association with the carcinoid flush (11).

Immunocytochemistry has demonstrated a number of peptides as well as serotonin in bronchial carcinoids. For example, adrenocorticotrophic-hormone, leuenkephalin, neurophysin, neurotensin, neuropeptide Y, pancreatic polypeptide and gastrin-releasing peptide have all been identified in bronchial carcinoids (see also separate section on Bronchial Carcinoids) (12-14).

Results of the above studies illustrate that many carcinoid tumors contain numerous polypeptides. With time and development of even newer techniques, it is likely that other neuropeptides will be localized and identified in carcinoids.

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CLASSIFICATION OF CARCINOIDS

Carcinoid tumors have been classified as foregut, midgut or hindgut tumors (1). Details of this classification and some of the identifying features of tumors in each classification are listed in Table 4.

TABLE 4. CLASSIFICATION OF CARCINOIDS (FROM REFS. 1 AND 2)

	FOREGUT	MIDGUT	HINDGUT
Localization	Stomach, duodenum, pancreas, bronchial tree	Jejunum, ileum, Meckel's diverticulum, appendix, ascending colon (rare)	Transverse, descending and sigmoid colon, rectum
Silver Affinity			
Argentaffinity[a,b]	-(+)	+	- (+)
Argyrophilia[c]	+(-)	+	- (+)
Secretory products	5-H Tryptophan, histamine, multiple peptides	5-H Tryptamine, bradykinin ?, prostaglandins ?, substance P, other peptides	Various peptides
Functional manifestations	Carcinoid syndrome can occur but is relatively rare, some tumors may have atypical carcinoid syndrome	Carcinoid syndrome occurs especially seconary to metastasis from small intestinal carcinoids	Carcinoid syndrome extremely rare

a (+) (-) signs in parentheses indicate exceptional cases.
b Argentaffinity-refers to the ability of carcinoid cells to take up silver salts.
c Argyrophilia - refers to the ability of carcinoid cells to deposit metallic silver only when an exogenous reducing agent is added to the reaction.

Approximately 85% of carcinoid tumors develop in the gastrointestinal tract with about 10% occurring in the lung. Those in the lung occur primarily as bronchial carcinoids [see Pulmonary (Bronchial) Carcinoids]. The remainder are found in organs such as the larynx, thymus, kidney, ovary, prostate and skin. As shown in Table 5, the most frequent location in the gastrointestinal tract is the appendix followed by the rectum and ileum.

TABLE 5. PERCENT DISTRIBUTION OF 1,867 CARCINOIDS BY SITE* (FROM REFS 3 AND 4)

Appendix	45%
Rectum	15%
Ileum	11%
Lung and bronchi	10%
Colon	5%
Small intestine (not specified)	5%
Cecum	3%
Stomach	2%
Duodenum	2%
Jejunum	1%

* Only frequencies of at least 1.0 percent are listed.

Percent carcinoids of all neoplasms in different organs is shown in Table 6. While less than 1% of all gastric tumors are carcinoids, 34% of all tumors of the small intestine are carcinoids.

TABLE 6. PERCENT OF ALL NEOPLASMS IN DIFFERENT ORGANS THAT ARE CARCINOIDS* (FROM REFS 3 and 4)

Appendix	77%
Small intestine	34%
Rectum and rectosigmoid	1%
Lung and bronchi	1%
Colon except appendix	<1%
Stomach	<1%

* Shown are data from 970 carcinoid tumors. A total of 2,837 cases were analyzed.

Carcinoids may be incidental findings at laparotomy or at autopsy (5). In the gastrointestinal tract, the tumor begins in the submucosa and extends outwards gradually involving the serosa, subsequently extending into the mesentary and adjacent structures. The overlying mucosa usually remains intact, although occasionally ulceration may occur. Rarely, does the tumor encroach on the lumen, but annular constricting lesions may occur resulting in obstruction of the bowel (5).

In over 50% of patients, carcinoid tumors are asymptomatic and in one series approximately 25% were discovered incidentally at the time of autopsy. Carcinoids are the most frequent of all endocrine gut tumors and are defined as a neoplasm by most pathologists because of their malignant potential (6).

As shown in Figure 1, the mean age of 225 patients with carcinoid tumors was

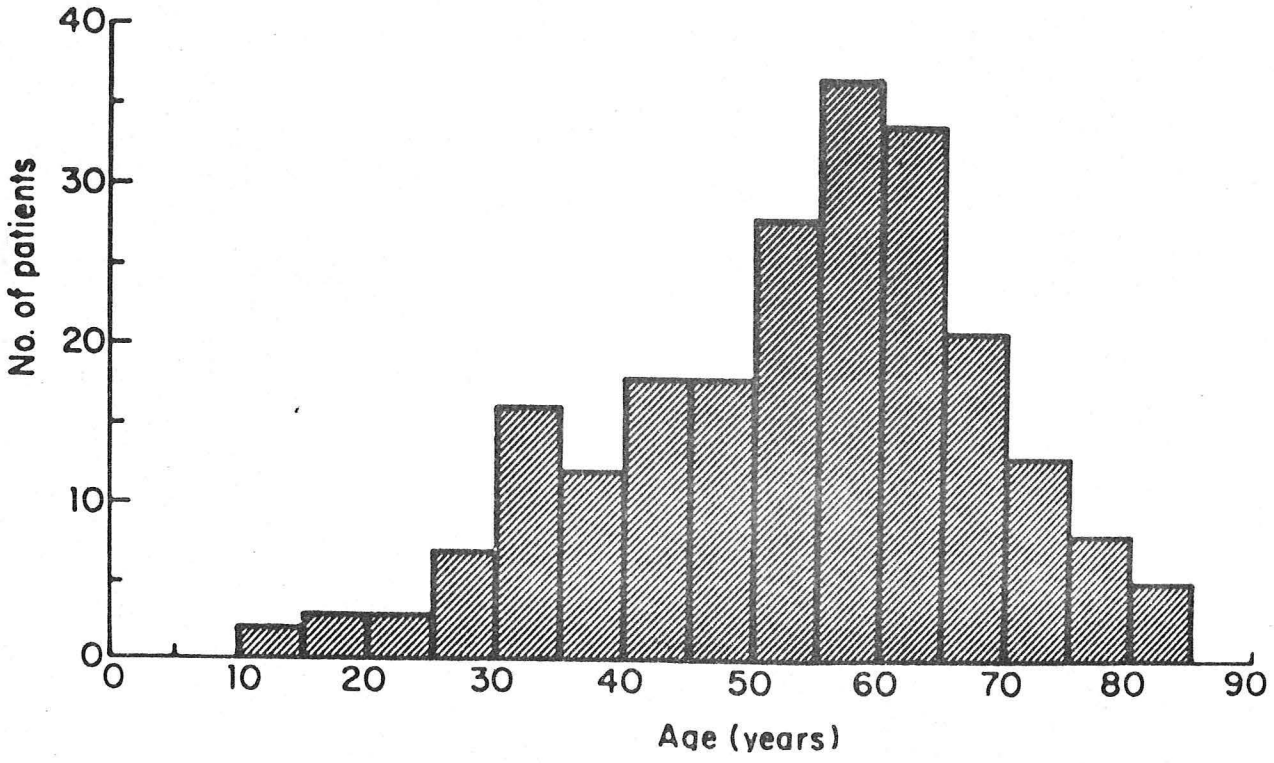

Figure 1. Histogram of the age distribution of 225 patients with carcinoid tumors (From Feldman, J.M., Ref.7).

53 years (range, 10 to 83 years) with the peak decade of occurrence between 50 to 60 years of age. Sixty-three percent of patients were men and 37 percent were women (7). The greater percentage of men in this particular series may have been related to the fact that many of the patients were from a VA Medical Center while in other series there has been a more equal distribution between men and women.

In another study (8), the patients' ages at the time of tumor detection ranged from 17 to 86 years, with an average of 53 years. The mean ages of patients with appendiceal carcinoids and bronchial tumors were significantly lower than the mean ages of those whose primary lesions were in the small bowel or colon. As in the other series, there were slightly more men than women (56 men vs 45 women) but the difference was not statistically significant.

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FOREGUT CARCINOIDS

Foregut carcinoids may arise in the esophagus (rare), stomach (see section on gastric carcinoids), duodenum (including ampulla of Vater), pancreas, biliary tract, bronchial tree and lung and thymus (1-3). Foregut carcinoids comprise a heterogeneous group of tumors which cannot be defined accurately because their morphologic characteristics are frequently the same as those of endocrine tumors of the pancreas (4,5). The distinction between carcinoid tumors of the pancreas and other endocrine tumors of the pancreas is frequently made on the basis of clinical presentation and not tumor morphology. For example, histologically, it is difficult to distinguish between insulinomas, glucagonomas, gastrinomas, VIPomas and carcinoid tumors. Foregut carcinoids for the most part appear identical to each other and to carcinoids from other locations as determined by conventional histologic methods. However, silver impregnation, ultrastructural studies and immunohistochemical techniques have shown a tremendous biological variability among these tumors.

Some foregut carcinoids are capable of producing a variety of peptide hormones. Gastric and duodenal carcinoids have been associated with parathormone production (6) and some carcinoids of the stomach and bronchus have secreted ACTH in association with clinically evident Cushing's syndrome (7,8). Other carcinoid tumors have released growth hormone, resulting in acromegaly (9,10), insulin associated with hypoglycemic episodes (11) and some have secreted calcitonin (12), vasopressin (13) or glucagon (14).

Foregut carcinoids usually are argyrophilic and only rarely argentaffin positive. The morphology of their secretory granules varies greatly when examined with electron microscopy. The most frequent electron microscopic appearance has shown a pattern of sparsely granulated cells containing small granules (120-180 nm in diameter) with round, electron-dense cores closely surrounded by a limiting membrane (4). This pattern is especially applicable to bronchial carcinoids.

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Specific Types of Foregut Carcinoids

Pulmonary and Bronchial Carcinoids

The study of pulmonary and bronchial carcinoids, so far, has not been as extensive as the study of gastrointestinal neuroendocrine cells and carcinoids (1). Pulmonary carcinoids were first described by Hamperl in 1937 (2) and the so-called endocrine cell, "clear cells," of the lungs were not described until 1949 (3). Carcinoids in the lungs are thought to be related to the neuroendocrine cells of the normal bronchial epithelium, the Kulchitsky's cells, just as gastrointestinal carcinoids are related to the neuroendocrine cells of the normal gastrointestinal mucosa (4,5).

Embryologically, pulmonary carcinoids are considered foregut tumors and generally are not stained by the argentaffin method but instead are stained by the argyrophil technique (6). They contain secretory granules when examined ultrastructurally. These carcinoids are thought to originate from the ductal epithelium of bronchial mucus glands. Pancreatic polypeptide-like immunoreactivity, serotonin-like immunoreactivity, bombesin-like immunoreactivity and ACTH-like immunoreactivity all have been identified in pulmonary carcinoids (1). Acromegaly and Cushing's syndrome due to secretion of growth hormone, growth hormone-releasing factor and adreno-corticotropin hormone or corticotropin-releasing factor also have been reported to occur occasionally in patients with bronchial carcinoids (7,8). Originally, the tumor was thought to be benign but later studies have shown an overall 5-year survival of about 50% (9). Survival may vary, however, with the type of bronchial carcinoid. Survival is much lower

when the histology is that of an atypical carcinoid than when the histology is typical (9). For example, in a series of 232 patients with carcinoid tumor of the lung reported from the Mayo Clinic, 11 percent were atypical (10,11). The five-year survival was 57% in these patients compared with a survival of 85-90% in another groups of patients with typical carcinoids (9). In general, bronchial carcinoids have a low degree of malignancy and hormonal symptoms are rare despite the fairly frequent occurrence of bioactive peptides and serotonin in the tumor.

The primary sites of pulmonary and bronchial carcinoids in 91 patients are shown in Table 7 (11).

TABLE 7. PRIMARY SITES OF PULMONARY AND BRONCHIAL CARCINOIDS IN 91 PATIENTS (REF. 11)

CARCINOID LOCATION	NO. OF PATIENTS
RIGHT	
Main bronchus	1
Intermediate bronchus	1
Upper lobe	15
Middle lobe	20
Lower lobe	15
LEFT	
Main bronchus	2
Upper lobe	9
Middle lobe	1[a]
Lingula	5
Lower lobe	22

a Situs inversus

D.E., 54 y/o man

Admitted to DVAMC with history of stone in left kidney; no symptoms relative to carcinoid

PA and Lateral Chest - 1½ x 1½ cm mass in RML

Bronchoscopy - no endobronchial lesion visualized

Surgical findings - well circumscribed nodule in area between the right upper and right middle lobes

Procedure - right middle lobectomy and partial right upper lobectomy

Pathology - carcinoid

Bronchoscopy appears to be the most useful diagnostic procedure and establishes the diagnosis preoperatively in 60 to 73% of patients (11,12). However, in the patient described above the lesion was not visualized by bronchoscopy yet was clearly present between the right upper and middle lobes at the time of surgery.

In performing bronchoscopy, care must be taken. Life-threatening hypotension has been reported as a complication of flexible fiberoptic bronchoscopy in a few patients with acute carcinoid syndrome (13) (see use of somatostatin analogue in prevention of carcinoid crisis).

In general, if a patient has a gastrointestinal carcinoid and the carcinoid syndrome, hepatic metastases are present to account for the symptoms. With extragastrointestinal carcinoids, symptoms of the carcinoid syndrome may be present but, because of venous drainage directly into the systemic circulation, this does not mean necessarily that the tumors are metastatic to the liver. In spite of this, the carcinoid syndrome is rare in patients with bronchial carcinoids (1). Most patients are asymptomatic indicating that the tumor is slowly growing and rarely hormonally active. However, some patients present with a cough, hemoptysis and lower respiratory tract infection (14). Occasionally, a pulmonary carcinoid will obstruct a bronchus and cause these symptoms. Laser therapy has been used in some patients to relieve the obstruction (personal communication, Lawrence R. Schiller, M.D.).

Radical removal of all tumor-bearing tissue is usually the treatment for carcinoid tumors of the lung (11). Adequate resection with frozen-section analysis of the resected margins is essential and any lymph node metastases should be removed. Complete removal of a lung rarely is necessary. In most patients lobectomy is the procedure of choice as in patient D.E. who had a right middle lobectomy and partial right upper lobectomy. Endoscopic removal of a carcinoid may be used in patients with high risk or those who require relief of respiratory obstruction (11).

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Peripheral Carcinoid and Oat Cell Carcinoma. This tumor is likely a type of foregut carcinoid. The morphologic appearance of these tumors may range from the appearance of typical carcinoids to the highly anaplastic oat cell carcinomas. There is controversy as to whether these tumors originate from the small basal cells of the bronchial and bronchiolar epithelium (1) or whether they arise like bronchial carcinoids from the endocrine cells of the same epithelium (2). The latter origin would explain why many oat cell carcinomas produce peptides. Other workers, however, believe that originating from endocrine cells is not a prerequisite for oat cell carcinomas to produce ectopic peptides (3). For example, the process of neoplastic cell replication and possibly normal cell replication is associated with "ectopic" protein or peptide synthesis. It is possible that the process of neoplasia per se is associated with rates of ectopic hormone synthesis above that of the normal cells or that cell replication rates per se are directly related quantitatively to peptide elaboration (3).

Atypical carcinoids and oat cell carcinomas are most frequently found in the lung although examples of oat cell type tumors have been reported in the esophagus, stomach, pancreas and upper small intestine (4). Some peripheral carcinoid tumors and oat cell carcinomas are not associated with a clinical hormonal syndrome (4). Whether these tumors do not release peptides into the circulation or release peptides which are incomplete or biologically inactive is not known (4,5).

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Gastric Carcinoids

J.J., 39 y/o lady

CC: Paresthesias, insomnia, left upper quadrant pain

Laboratory: MCV - 104 μm^3

Serum B_{12}-88 pg/ml (normal, 200-900)

Serum gastrin - 1030 pg/ml (normal, <100)

Gastric Acid - BAO - 0 mmol/h
PAO - 0 mmol/h

Schilling Test I - 0% (normal, $\geq$ 8%)
II - 8% (normal, $\geq$ 8%) (with Intrinsic Factor)

UGI: Fundic nodularity

Oct. 1986: Total gastrectomy, no metastases

Pathology: Carcinoid polyps

Micro - carcinoids

Hyperplasia of gastric endocrine cells

Immunofluorescence: + gastrin (not in polyps)

+ chromagranin

- serotonin

This patient has carcinoid polyps in the stomach, micro-carcinoid tumors of the stomach and hyperplasia of enterochromaffin-like (ECL) cells. The patient had achlorhydria, pernicious anemia, an abnormal Schilling Test and an increased serum gastrin concentration, clinical findings that are present in many patients with gastric carcinoids. Patients also may have abdominal pain, anemia, hemetemesis or melena. Massive bleeding has been reported on occasions. On barium x-

ray of the stomach, carcinoids frequently present as polypoid filling defects which may have central ulcerations (1). Carcinoids usually do not ulcerate when located elsewhere in the gastrointestinal tract, but ulceration is relatively common in the stomach. The differential diagnosis includes adenomatous polyps, carcinoma, leiomyoma and lymphoma (1).

Gastric carcinoids, recognized first by Askanazy (2), are small, slow-growing, submucosal tumors, which may be single or multiple and comprise about 1-3% of all carcinoid tumors. Gastric carcinoids rarely synthesize serotonin since they usually lack the enzyme, histidine decarboxylase (3). Most gastric carcinoids are believed to develop from the nonargentaffin, argyrophil enterochromaffin-like cell (ECL) which is the major endocrine cell type in the normal fundic mucosa (4-7). Gastric carcinoids, however, can occur either in the fundus or body of the stomach (8). The hormonal products of this cell are still unknown. Although they frequently metastasize (9-13), gastric carcinoids are most often "endocrinologically silent" without signs of the classical carcinoid syndrome (9). Gastric carcinoids have metastasized in as many as 17 to 39% of patients (14) and an incidence of regional spread of tumor as high as 55% was reported in one series (13).

Although the hormonal products of the ECL cell, per se, are unknown, a number of peptides have been analyzed immunohistochemically in multiple gastric carcinoids. The peptides that have been found by this technique are listed in Table 8.

TABLE 8. PEPTIDES ANALYZED IMMUNOHISTOCHEMICALLY IN MULTIPLE GASTRIC CARCINOIDS (FROM REF. 8)

Adrenocorticotrophic hormone	Met-enkephalin
Insulin	Motilin[a]
Calcitonin[a]	Neurotensin
Parathyroid hormone[a]	Secretin
Bombesin[b]	Somatostatin[a,b]
Cholecystokinin	Substance P[b]
Corticotrophin-like intermediate peptide	Vasoactive intestinal peptide[b]
Endorphin	S 100 (glia cell marker)
Gastric inhibitory peptide	Serotonin
Glucagon[a]	5-Hydroxytryptamine

a Also analyzed by radioimmunoassay on serum or plasma.
b Also analyzed by radioimmunoassay on fresh-frozen tumor tissue.

In addition to the association between gastric carcinoids, a relationship also has been reported between atrophic gastric mucosa and enterochromaffin-like (ECL) cell hyperplasia (3,15-18). It has been suggested that some of the factors that increase the risk of adenocarcinoma in the stomach also effect ECL cells (3). For example, achlorhydria, with or without pernicious anemia, may be associated with both gastric carcinoids and adenocarcinoma of the stomach.

Endocrine Cell Hyperplasia, Carcinoid Tumors and Pernicious Anemia. As of 1985, thirty patients had been reported with pernicious anemia and gastric carcinoids (8). Fifteen patients were women, 14 were men and in one patient the sex was not given. Of the 30 patients, 22 had multiple gastric carcinoids and 26 were located either in the fundus or body of the stomach.

Endoscopic screening was carried out in a recent review of 123 patients with pernicious anemia. Four patients had a solitary gastric carcinoid and 1 patient had multiple gastric carcinoids (8). In this same experiment, quantitative histologic studies of multiple standardized biopsy specimens were performed. A significantly increased number of fundic mucosal argyrophil, endocrine cells were found in the 40 patients with pernicious anemia when compared with 15 patients with simple fundic gastric atrophy. In the opinion of these authors, all carcinoid tumors should be radically removed either by endoscopy or at laparotomy (8). If the lesions are small, endoscopic removal is probably appropriate but some recommend regular follow-up examinations.

Atrophic Gastritis, Hypergastrinemia, Enterochromaffin-like Cell (ECL) Hyperplasia and Gastric Carcinoids. There are two major forms of atrophic gastritis, types A and B (19). In type B, the fundus and antrum are both affected. Because the antrum is involved, the gastrin cell mass is reduced and serum gastrin concentration is not increased. In contrast, atrophic gastritis type A (gastritis involving the fundus and body but sparing the antrum), is associated with a proliferation of gastrin producing cells (G cells) in the antral mucosa (19-28). Since the antrum is not involved with gastritis, hypochlorhydria or achlorhydria leads to hyperplasia of gastrin cells and to increased serum gastrin concentration. It has been postulated that the trophic effects of constantly increased serum gastrin levels might predispose the corpus mucosa to endocrine cell hyperplasia and ultimately to development of small nodules of argyrophil cells, "microcarcinoidosis," and to carcinoid tumors. In addition to the above findings, Type A gastritis is associated with pernicious anemia in a large percentage of patients. These patients may also have endocrine disorders such as hypothyroidism, diabetes mellitus, decreased adrenal function and hyperthyroidism.

Evidence supporting the role of the trophic effect of constantly increased serum gastrin levels on the proliferation of fundic endocrine cells is derived from the observation that diffuse and nodular hyperplasia of fundic endocrine cells occurs exclusively in patients with atrophic gastritis Type A and in patients with Zollinger-Ellison syndrome. Both conditions are associated with long-standing hypergastrinemia. Furthermore, as is discussed in more detail below, hypergastrinemia induced in female rats by life-long treatment with omeprazole or potent H_2-receptor antagonists, led to development of fundic carcinoid tumors (29-31). In contrast, antrectomized rats with decreased gastrin levels showed a decrease in fundic argyrophil cells (32).

Gastrin and Trophic Control of Gastric Mucosa. Two gastrointestinal hormones, gastrin and cholecystokinin, are thought to be important growth promoting agents in the digestive tract. As shown in Figure 2, the targets for the growth promoting effects of gastrin are the fundus and upper body of the stomach while for cholecystokinin, the targets are the pancreas and biliary tree (33).

As mentioned above, when acid secretion is absent as in pernicious anemia or is suppressed markedly by powerful antisecretogogues, stimulation of gastrin occurs. Omeprazole inhibits acid secretion markedly by inactivating the H^+/K^+ ATPase enzyme which is the proton pump for hydrogen ions and is located on the

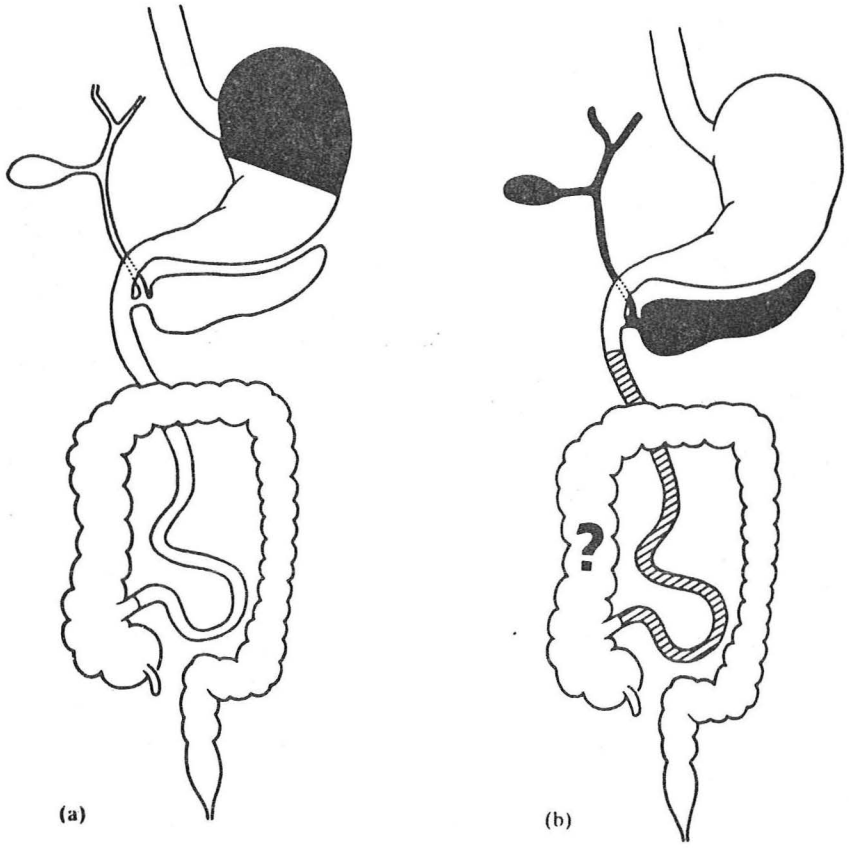

Figure 2. Suspected target tissues for the growth promoting effect of (a) gastrin and (b) cholecystokinin. Known targets are shown in black, controversial targets are hatched or labelled with a question mark (from Ref. 33).

luminal surface of the acid secreting, parietal cell. When omeprazole was administered to rats for a period of 24 months, diffuse endocrine cell hyperplasia and focal neoplasia, characterized as carcinoids, developed in the body of the rat stomachs. In the animals receiving the highest-dose, 40% of the female rats and 10% of the male rats developed carcinoids (34). The hyperplastic and neoplastic cells were identified as ECL cells by silver staining and by electron microscopy. The ECL cells are endocrine cells known to contain large amounts of histamine and histadine decarboxylase (HDC) in the rat and to be functionally and trophically controlled by gastrin (35).

A study was designed to determine whether ECL cell proliferation occurred after prolonged treatment with antisecretogogues and to determine the mechanism for the proliferation and its reversibility (30). Unoperated female rats were subjected to daily oral therapy with either omeprazole, ranitidine, an H_2-receptor antagonist, or a control. Antrectomized rats were treated with omeprazole or control.

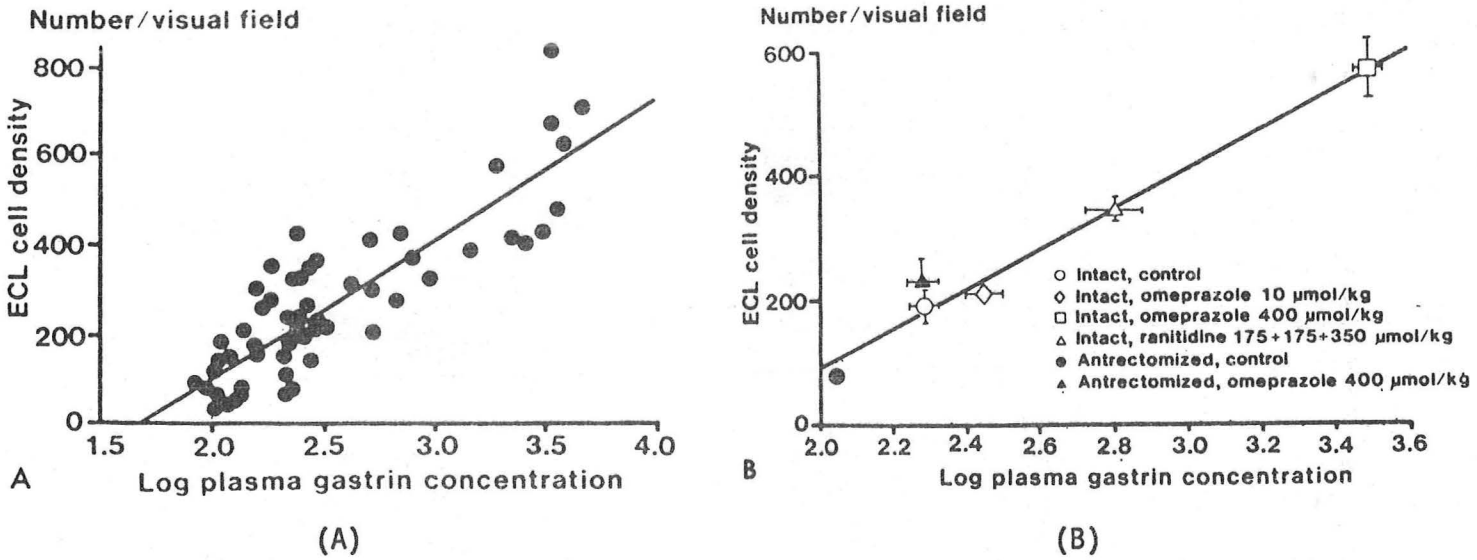

Figure 3. Correlation between plasma gastrin levels and ECL density in oxyntic mucosa after 10 weeks treatment with omeprazole, ranitidine or vehicle. (A) Individual data from all groups (r=0.86, p=0.0001). (B) Group mean values ± SEM, r=0.99; significance level = 0.001 (From Ref. 30).

After 10 weeks of therapy, plasma gastrin levels were increased in unoperated rats treated with the high dose omeprazole or ranitidine and gastrin concentrations were low in antrectomized controls. A close correlation (r = 0.86) was found between the gastrin level and the mucosal enterochromaffin-like cell density in all groups (Figure 3). Since ECL cells in rats produce histamine and histidine decarboxylase, this too was measured. There also was a close correlation between the level of histamine, histidine decarboxylase and ECL density. During a recovery period of 10 weeks, following the 10-week treatment period, the enterochromaffin-like cell density and histamine concentration decreased by 30-40% in the rats treated with the high dose of omeprazole. Plasma gastrin levels also returned to control values during recovery. Results of this study suggest that the observed changes in ECL density are related to plasma gastrin levels and that they are reversible. Because ECL cell hyperplasia was correlated with serum gastrin concentrations, it was concluded that neither omeprazole or H_2-receptor antagonists are likely to produce ECL hyperplasia independent of their altering serum gastrin concentrations. It also was the belief of the authors of this paper that the development of carcinoid tumors in the stomachs of rats after 2 years of treatment with omeprazole was the result of sustained hypergastrinemia induced by long-lasting inhibition of acid secretion and not due to the drug, per se.

Man, in contrast to the rat, contains both enterochromaffin cells (EC) and enterochromaffin-like cells (ECL cells). The physiological role for ECL cells in man is not known. In the rat, ECL cells clearly have the ability to synthesize and store histamine whereas this ability is not present in human ECL cells. Spontaneous neoplasia of the ECL cell has been described in man. Gastric carcinoids may be comprised of ECL cells, gastrin cells, cells containing pancreatic polypeptide or cells producing hormones ectopic to the gut such as adrenocorticotropin and melanocyte stimulating hormone. Gastric carcinoids frequently contain several types of endocrine cells. The tumors are located

usually in the fundus or upper body of the stomach. If they are less than 2 cm in diameter, they generally are asymptomatic, non-invasive and do not metastasize. However, about 25-50% of gastric carcinoids metastasize.

It is difficult not to relate hypergastrinemia with the hyperplasia and neoplastic transformation of gastrin-sensitive endocrine cells in the stomach, including ECL cells. This is true whether in experimental animals such as rats in which acid secretion is suppressed by drugs such as omeprazole or in patients with increased serum gastrin concentrations due to Zollinger-Ellison syndrome or pernicious anemia. A high pH may enhance the development of carcinoid tumors but advancing age may be another factor.

In an editorial in GUT, Penston and Wormsley questioned the hypothesis that hypergastrinemia secondary to achlorhydria led to ECL hyperplasia and carcinoid tumors (36). They admitted that the inability to secrete acid and development of hypergastrinemia might predispose to proliferation of gastric ECL cells since similar proliferation occurred in rats after portocaval shunt and in patients with gastrinoma. However, they stated that this sequence of events may not be essential for hyperplasia to develop. Regardless of whether or not there is a relationship between gastrin and ECL hyperplasia, the authors of this editorial raised questions as to whether the relationship between achlorhydria, hypergastrinemia, ECL hyperplasia and carcinoid tumors was causal. It seems reasonable to assume, at least for the moment, that hypergastrinemia might play a role in development of ECL hyperplasia and gastric carcinoid tumors at least in some patients.

Most physicians recommend removing gastric carcinoids either by endoscopy or surgery. If there are only one or a few carcinoids, then removal usually is relatively easy and should be carried out unless the patient is a poor operative candidate. Whether patients should have a total gastrectomy for multiple gastric carcinoids (as in J.J.) is controversial. If hypergastrinemia is eventually proven to be the cause of gastric carcinoids in patients with atrophic gastritis, antrectomy might become the procedure of choice.

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Carcinoids of the Ampulla of Vater, Biliary Tract, Duodenum,and Pancreas. Biliary tract carcinoids represent about 0.2-2% of all carcinoids in the gastrointestinal tract (1). They have been found in the gallbladder, the common bile duct and the ampulla of Vater (2,3). Patients with tumors of the ampulla present usually with painless, progressive jaundice (2) although some can develop acute pancreatitis (4,5). Bile stasis appears to be the most common presenting symptom of ampullary tumors (1,6). Symptoms of the carcinoid syndrome are rarely, if ever seen, and serotonin and 5-HIAA levels are usually normal although a rare patient with ampullary carcinoid exhibiting the carcinoid syndrome has been reported (7). Even though ERCP may fail to make the diagnosis in some patients, it appears to be the method of choice for making a proper diagnosis and to be the initial endoscopic interventional test. If initial biopsies are negative for carcinoid, the diagnosis can be made occasionally by repeated intrapapillary endoscopic biopsies (8). The best opportunity for a positive tissue diagnosis occurs when biopsies are taken from the edges of the papillotomy site or snare biopsies are obtained from a protruded papilla. In many patients it is difficult to differentiate between ampullary cancer and ampullary carcinoid on macroscopic appearance. The yellowish appearance of carcinoids may be recognized but papillary carcinomas may also appear yellow due to bile staining. Usually, a definite diagnosis can be made only with special staining techniques. For example, in one case immunoperoxidase stains identified the neoplasm as neuroendocrine in origin and electron microscopy confirmed the presence of neurosecretory granules (9).

The prognosis of ampullary tumors is difficult to establish. It is very important to differentiate ampullary carcinoid tumors from ampullary carcinoma prior to surgery because in a number of patients carcinoid tumors have been misdiagnosed as carcinoma of the head of the pancreas and radical surgical procedures have been performed unnecessarily (10). The recommended treatment for ampullary carcinoids is wide local excision with reimplantation of the biliary and pancreatic ducts (3). Local resection is recommended even when metastases are present because of the slow progression of the disease (3,10). Some authors recommend also removing regional areas of metastasis (11). Others, however, have reported prolonged survival even without treatment, thus leading to controversy as to whether to remove the tumors. Surgery usually is recommended, especially in children and young adults (6). In patients with contraindications for surgery or patients with metastases, palliative treatment with an endoscopically placed biliary endoprosthesis or an extended papillotomy should be considered (6). Ampullary tumors have responded to chemotherapy although response to chemotherapy is variable (12). Improvement in symptoms also has been reported during steroid treatment and after radiation therapy (7). I-131-meta-io-benzyguanidine has provided some benefit in a few patients with metastases (13) (see section on Therapy of Carcinoid Syndrome).

The normal duodenal mucosa also contains numerous endocrine cells (14). Tumors derived from these cells have been reported. Among these, two entities are most prominent: gastrinomas, generally associated with the Zollinger-Ellison syndrome and somatostatinomas. The latter tumors have seldom been associated with the somatostatinoma syndrome as described in pancreatic somatostatinomas.

Carcinoid tumors of the pancreas are extremely rare. In two reviews of gastrointestinal carcinoids involving more than 3000 cases there were no pancreatic carcinoids (15,16). However, a case of chronic pancreatitis and pseudocyst formation secondary to carcinoid tumor of the pancreas has been reported recently (17).

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Carcinoid of the Gallbladder. Primary carcinoid tumors of the biliary tract are rare. In a series of 2,837 cases of carcinoid tumors from the files at the National Cancer Institute, only 2 patients with carcinoid tumors in the biliary tract were reported: one carcinoid of the gallbladder and the other of the bile duct (1). As of 1983 (2), 21 patients with biliary tract carcinoids have appeared in the literature and 17 of them were carcinoids of the gallbladder. Occasionally, gallstones are associated with carcinoids of the gallbladder. In 21 carcinoid tumors of the gallbladder, including one composite type tumor (carcinoid plus adenocarcinoma), 6 patients were found to have gallstones (3). The prognosis of carcinoids of the gallbladder is relatively grim. In one review, the majority of patients died within one year after surgery for gallbladder disease (3).

While carcinoid syndrome rarely develops, there have been two reported cases of gallbladder carcinoids which demonstrated hormonal activity. One patient had carcinoid syndrome (4) while the other patient had Cushing syndrome (5). In both patients hepatic metastases were found at the time of surgery.

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Other Foregut Carcinoids

Carcinoid Tumors of the Middle Ear. Several patients have been reported with carcinoid tumors of the middle ear (1,2). While the origin of these tumors are not well understood, the tumors most likely originate from preexisting neuroendocrine cells or a primitive precursor cell. The facts that argyrophilic granules were demonstrated by Grimelius stain and neurosecretory-type granules were present on transmission electron microscopy suggest that carcinoids of the middle ear are of foregut derivation. Pancreatic polypeptide has been identified in tumors from 2 patients with carcinoids of the middle ear (2). Stains have been performed for a number of other neuropeptides but additional substances have not been found.

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Carcinoids of the Thymus. Carcinoids of the thymus were described first in 1972 (1) and fewer than 100 cases have been reported. So far, there are no reports of carcinoid syndrome developing as a consequence of carcinoid tumors of the thymus (2,3). Most patients are men and the median age is about 43 years.

Carcinoid tumors of the thymus, like other carcinoid tumors, are slow-growing neoplasms that have the capacity for direct metastasis but, rarely, for implantation metastasis. The most common site of distant metastasis is bone, where the tumor is mainly osteoblastic (4,5).

Wide excision of the tumor is the most common treatment (6) while some patients have been treated with postoperative radiation (7). Chemotherapy has been of limited effectiveness (8,9). As with thymoma A, carcinoid tumor of the thymus may recur as long as ten years after initial resection. Thus, prolonged follow-up of all patients is indicated.

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MIDGUT CARCINOIDS

Carcinoids of the jejunum, ileum and appendix comprise a very homogenous group of tumors both morphologically and functionally (1). In contrast, their biological behavior differs in several respects. For example, appendiceal carcinoids rarely show malignant features and frequently are incidental findings at surgery or autopsy (see section on Appendiceal Carcinoids). On the other hand, up to one-half of jejunal and ileal carcinoids show malignant behavior at some time during their course.

Midgut carcinoids appear as yellow-grayish masses which often are located in the submucosa and abut into the lumen of the viscus. Midgut carcinoids appear as nests and sheets of uniform polygonal cells with abundant cytoplasm and round central nuclei, separated by slender strands of fibrovascular stroma. Mitoses are rare and cellular atypia is found infrequently (1). Midgut carcinoids usually are argentaffin and argyrophilic positive after silver impregnation (Table 4). On electromicroscopic examination of midgut carcinoids, the cells are characterized by a relatively large amount of cytoplasmic secretory granules. These granules usually are polarized toward the basal or vascular portion of the tumor. The carcinoid tumor cells resemble very closely the normal enterochromaffin (EC) cells which are found in large numbers in the mucosa of the small and large intestine as well as in the appendix.

Without metastasis to the liver, primary midgut carcinoids are usually silent clinically. When massive metastases of midgut carcinoids occur to the liver or to the lung, the carcinoid syndrome develops (1). A few midgut carcinoids produce calcitonin, VIP, ACTH, and perhaps other neuropeptides. The exact meaning of the production of these seemingly ectopic peptides in midgut carcinoids is not clear.

Specific Types of Midgut Carcinoids.

Small Intestinal Carcinoids. The small bowel is the most common location for carcinoids of clinical significance (1) and the ileum is the most frequent site of small bowel carcinoids (2). Small intestinal carcinoids may present as multiple nodules within the ileal wall or may be discrete tumors within the ileal lumen. They also may occur in the jejunum. The most common clinical presentation for small bowel carcinoids is periodic abdominal pain which is frequently consistent with intermittent small bowel obstruction (see below). Intussusception also can cause abdominal pain. Gastrointestinal bleeding from small bowel carcinoids is uncommon and only rarely do these lesions ulcerate. However, endoscopy has been used in at least one patient to diagnose a bleeding ileal carcinoid (3). Massive bleeding from small bowel carcinoids has been reported (3). An abdominal mass is present in about 20% of patients (1). Sometimes the carcinoid syndrome will be the initial manifestation of a small intestinal carcinoid.

Frequently, carcinoid tumors infiltrate the mesentery and induce a desmoplastic response that results in kinking and obstruction of adjacent bowel loops. The fibrotic reaction in the mesentery is responsible for the classic findings on barium examination in patients with carcinoid tumors which include fixation and separation of bowel loops, luminal narrowing and in some patients intestinal obstruction (4,5). Angiography also may show irregularity, kinking and occlusion of mesenteric blood vessels (6). Mesenteric involvement is shown generally on CT as a soft-tissue mass (7).

Symptoms may be present for a prolonged period before diagnosis of a small bowel carcinoid is made. In a series from the Mayo Clinic (1), the median time from the onset of symptoms to diagnosis was over 2 years with a range extending to as long as 20 years. Frequently, the diagnosis is so elusive that the patient consults several physicians until the diagnosis is finally established. By this time, frequently, it is too late. Fifty percent of the symptomatic patients have unresectable disease. In one series there was a relatively high incidence (18%) of metastases from primary ileal tumors that were smaller than 1 cm (8).

In the series from the Mayo Clinic the incidence of metastasis was related to the size of tumor. This is illustrated in Figure 4 below.

Primary carcinoid tumors of the gastrointestinal tract are small lesions that are difficult to detect with routine barium x-rays (9,10). CT and ultrasound have been used to identify primary and metastatic carcinoid tumors although the success has not been very good at finding the lesions. Computed tomographic (CT) scans were no more sensitive in one series for detection of primary tumors than were other radiographic examinations (7). The primary tumor was identified in only 2 of 9 patients scanned before surgery. No primary site could be found even at laparotomy in 4 of the 9 patients. Furthermore, the CT appearance of mesenteric, lymph node, and liver metastases is not specific for

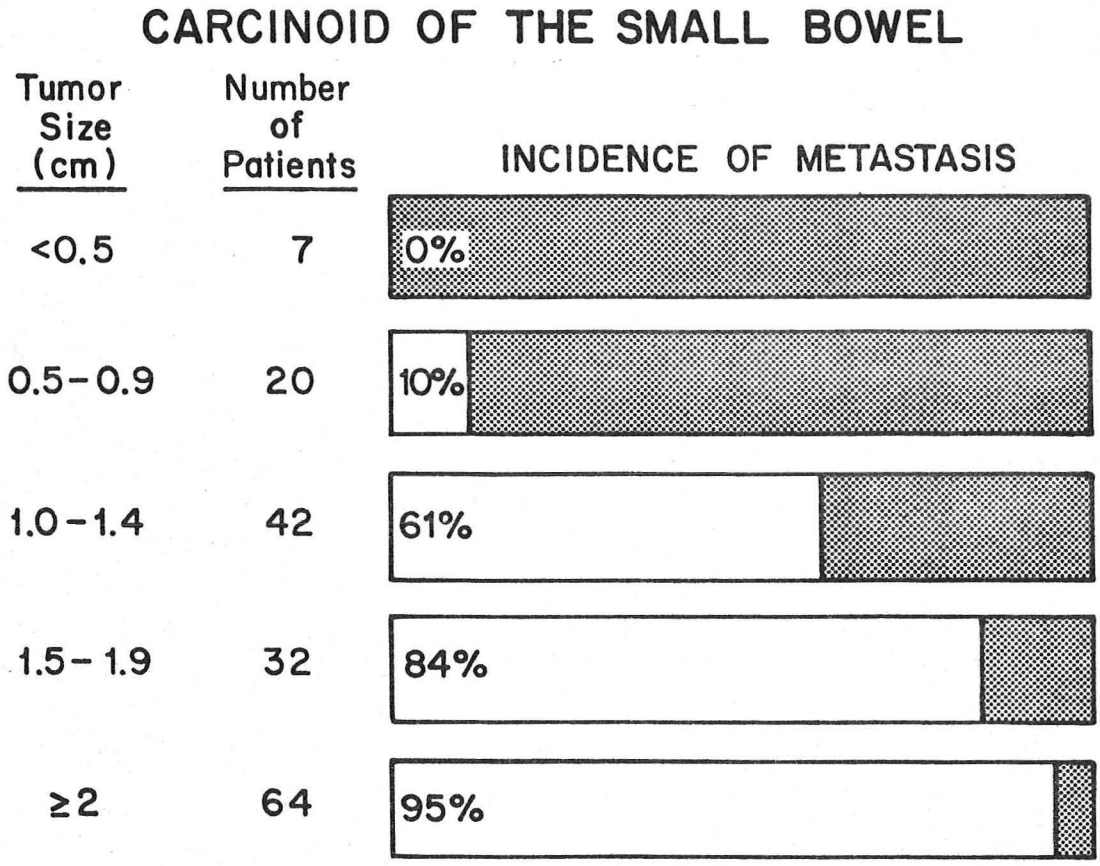

Figure 4. Incidence of metastasis of carcinoid of the small bowel related to tumor size (from Ref. 1).

carcinoid tumors (7). Similar findings can be seen with retractile mesenteritis, Crohn's disease, peritoneal mesothelioma, metastatic disease (e.g., ovary or colon), and lymphoma (8-10). However, a soft tissue mass in the mesentery of the right lower quadrant displacing surrounding bowel loops, with or without adenopathy and/or liver metastasis, should suggest the diagnosis of carcinoid tumor (7).

The likelihood of cure for small bowel carcinoids is relatively high for patients in whom all visible malignant disease can be resected. However, even when disease is localized to the bowel wall, recurrences develop. In patients with resectable nodal metastasis, follow-up and prognosis for cure is excellent at 5 years with 80% of patients free of disease (1). This figure may be misleading, however, since in the Mayo Clinic series only 23% of patients were actually recurrence free at 25 years (1).

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Carcinoid of the Appendix. Carcinoids of the appendix are found in 0.3 to 0.7% of patients at the time of appendectomy (1-3). They occur usually in young adults. With advancing age, their incidence decreases much more rapidly than might be expected by the frequency of appendectomy in the general population. However, as far as, carcinoid tumors, in general, are concerned, appendiceal carcinoids are relatively common. Prior to 1970, only 35 patients with metastatic carcinoid of the appendix were reported in the literature (3). Since 1970, eleven additional patients with metastases from the appendix have been reported, including a patient reported by Thirlby and colleagues from Dallas in 1984 (4).

Overall, appendiceal carcinoids represent about 45% of gastrointestinal carcinoid tumors (4). In 46 patients with metastatic appendiceal carcinoids, 28 had regional lymph node metastases and 18 had distant metastases with four reported deaths. Carcinoid syndrome has been reported in a few patients due to metastatic appendiceal carcinoid tumors. All distant metastases have occurred in patients with tumors greater than 2 cm (1).

A right colectomy has been recommended for appendiceal carcinoids with lymphatic invasion (5,6) or carcinoids of the appendix with mesoappendiceal involvement (7). Some think that this may be overly aggressive therapy unless tumor is present at the margin of resection. Also, right colectomy is probably not indicated in patients with carcinoids of the appendix, less than 2 cm in size, since there are no reported cases of systemic metastasis occurring after appendectomy for a carcinoid of this size. Patients with tumors greater than 2 cm or patients with carcinoids of the appendix who have residual tumor at the margin of resection should have a right colectomy (4).

Mucinous carcinoid tumors of the appendix are an uncommon variant of appendiceal carcinoid and patients may present clinically with ovarian metastases (8). Several patients have been reported with bilateral ovarian Krukenberg's tumors from this special type of neoplasm. The primary tumors in the appendix are a composite neoplasm with histologic features of both carcinoid and adenocarcinoma (9). Thus, these tumors have been labeled adenocarcinoids to designate the entire group of tumors. These special composite tumors exhibit a biologic behavior that appears to be more aggressive than conventional appendiceal carcinoids but less aggressive than appendiceal adenocarcinomas (10). Ovarian metastases usually are associated with widespread abdominal metastases. It appears, at least in some patients, that these appendiceal adenocarcinoids are composed of a bimodel population of mucus and enterochromaffin cells that have the ability to metastasize independently. The goblet-cell component has a propensity to metastasize to the ovary, resulting in ovarian lesions indistinguishable from typical Krukenberg's tumors (9). Since the appendiceal component may be overlooked, some authors recommend that an appendectomy be performed routinely in patients with Krukenberg's tumor of the ovary and in patients in whom no grossly obvious primary neoplasm can be found (9).

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HINDGUT CARCINOIDS

These carcinoids occur with relative frequency in the rectum but are rare in the colon. Usually, rectal carcinoids are diagnosed incidentally during routine rectal examination. Rectal carcinoids appear as rounded, somewhat elastic masses located in the submucosa and are covered by a reddened, sometimes bleeding mucosa (1). Most rectal carcinoids are small and are less than 1 cm in diameter. They usually are restricted to the submucosa although a few will consist of larger, sometimes ulcerated, lesions with a malignant appearance and a tendency to spread or metastasize. Local excision is usually adequate for smaller tumors but wide resection and careful exploration are essential for the larger, more malignant lesions.

Microscopically, hindgut carcinoids have the characteristic arrangement of nests and cords of cells. Hindgut carcinoids usually do not take up silver stains although, using special techniques, a few cells will take up the stain (2). Cytoplasmic secretory granules likely containing neurohormonal peptides are sometimes seen by electron microscopy of the cells in patients with rectal carcinoids (see Table 3).

Most hindgut carcinoid tumors are not active clinically. Patients with malignant hindgut carcinoids occasionally have 5-hydroxy-indole amines in the circulation (3) and immunohistochemistry has identified several peptides in the tumors. While metastatic rectal carcinoids have been associated with development of the carcinoid syndrome, this is extremely unusual (4). In one patient, 17 small tumors of the rectum were discovered, the largest of which measured less than 1 cm in diameter (5). This was an unusual patient despite the small size of the tumors. There were multiple metastases to regional lymph nodes. Both primary tumors and metastases were strongly argentaffin positive and most tumors and metastases contained several biologically active substances such as serotonin, somatostatin and glucagon-like immunoreactivity.

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Specific Types of Hindgut Carcinoids

Carcinoid of the Rectum. Rectal carcinoids are found in about one in 2,500 proctoscopic examinations (1). These tumors appear usually as a small yellow-gray, submucosal nodule. They are found usually in middle-aged adults. Most rectal carcinoids occur on the anterior and lateral walls of the rectum in a very small zone between 4 and 13 cm above the dentate line. While they appear histologically like other carcinoids, they do not stain with silver (in line with most hindgut carcinoids), and they rarely show evidence of serotonin production. This likely explains why they do not cause the carcinoid syndrome even though they do metastasize occasionally. About 80% of rectal carcinoids are less than 1 cm in diameter and few are greater than 2 cm. If a rectal tumor is less than 1 cm, it rarely if ever metastasizes. If the rectal tumor is greater than 2 cm, it metastasizes frequently. If the carcinoid is less than 1 cm in diameter, the tumor should be removed by local excision or fulguration (1). Wide local excision is recommended for all lesions measuring 1 to 2 cm to determine fully the depth of invasion of the tumor (1). Radical surgery has been suggested if rectal carcinoids are greater than 2 cm in size or tumors are less than 2 cm but have invasion of the muscularis propria (2-4).

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Carcinoid of the Ovary. Primary ovarian carcinoids were reported first in 1939 (1) and most of the tumors have been found in association with ovarian teratomas (2). Ovarian carcinoids are extremely rare and functioning, non-metastatic tumors may produce all or some of the features of the carcinoid syndrome, including diarrhea, facial flushing, bronchospasm and right sided cardiac lesions. Almost one-half of ovarian carcinoid tumors reported in the literature

have produced symptoms of carcinoid syndrome (3). Serotonin has been purported to mediate the systemic effects of these neoplasms, and their metabolite, 5-HIAA, has been the usual marker for the presence of an active, secreting tumor. Substance P levels also have been elevated in an occasional patient with a carcinoid tumor of the ovary. Thus, this peptide also may be a mediator of symptoms of carcinoid syndrome in some patients with ovarian carcinoids (4). Simple salpingo-oophorectomy is curative if the tumor is a primary carcinoid of the ovary (4). Recurrent tumors are rare following oophorectomy.

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SPECIAL CONSIDERATIONS

Carcinoid Tumors and Neurofibromatosis

Carcinoids have occurred in several patients who also have neurofibromatosis. In most of these patients, the tumors occur in the duodenum, ampullary area or in other parts of the small intestine. The case histories of patients from one series are summarized in Table 9.

The patient population shown above was equal in sex distribution, with a mean age of 54.3 years. None of the 6 patients had the carcinoid syndrome. Four of these 6 patients with von Recklinghausen's Disease had a carcinoid located at the ampulla of Vater. Additional patients have been reported in which there was an association between duodenal and/or ampullary carcinoids and neurofibromatosis. Because of the rarity of the association, the relative predominance of ampullary carcinoids among patients with von Recklinghausen's Disease must be more than pure coincidence (6). One possibility is that those patients with von Recklinghausen's Disease were diagnosed because the neurofibroma was in a location that caused obstructive jaundice, while other patients with carcinoids who also have von Recklinghausen's Disease are undiagnosed because they are asymptomatic. It is possible also that a common embryologic or microenvironmental reason explains the appearance of neurofibromatosis and a tumor of the ampulla of Vater. In another patient with duodenal carcinoid and neurofibromatosis, the tumor contained both calcitonin-producing tumor cells and extracellular amyloid (7).

TABLE 9. SUMMARY OF CASES (FROM REF. 1)

CASE	AGE/ SEX	LOCATION OF CARCINOID	MANIFESTATIONS OF VRD	TREATMENT	OUTCOME	AUTHOR	YEAR/ REF
1	72/M	Duodenal	Cutaneous and visceral neurofibromatosis; pheochromocytomas	None	Died	Lee	1970 (2)
2	34/F	Two duodenal tumors & one malignant ampullary tumor	Cutaneous and intestinal neurofibromatosis	Pancreaticoduodenectomy	Alive & NED at 18 months	Weichert	1971 (3)
3	78/F	Ileum	Cutaneous and intestinal neurofibromatosis; cafe-au-lait spots; kyphoscoliosis	Ileal resection	Unknown	Arnesjo	1973 (4)
4	30/M	Benign ampullary tumor	Cutaneous neurofibromatosis; cafe-au-lait spots	Biliary diversion	Recovery	Barber	1976 (5)
5	53/F	Malignant ampullary tumor	Cutaneous neurofibromatosis; cafe-au-lait spots	Biliary diversion	Alive & NED at 18 mons	Johnson	1981 (6)
6	59/M	Malignant ampullary tumor	Cutaneous neurofibromatosis; cafe-au-lait spots	Pancreaticoduodenectomy	Died after 18 months from metastatic disease	Hough	1983 (1)

NED: No evidence of disease
VRD: von Recklinghausen's Disease

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Multiple Endocrine Neoplasia I and II Syndrome and Carcinoid Tumors

The association of carcinoids with multiple endocrine neoplasia (MEN) was first reported in 1953 (1). Carcinoids have been described in association with both MEN type I and type II syndromes and most carcinoids in patients with MEN I or II syndromes are of foregut origin (2). The patient described by Underdahl, et al was 1 of 8 original patients in the description of MEN type I (1). The patient had a metastatic bronchial carcinoid, 2 large hyperplastic parathyroid glands, hypoglycemia and peptic ulcer disease. A patient also was described who had a duodenal carcinoid associated with parathyroid hyperplasia, Zollinger-Ellison syndrome, and pituitary hyperplasia. Later, a patient was reported with duodenal carcinoid associated with MEN type II. This patient also had multiple pheochromocytomas (3).

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Carcinoid Tumors in Patients With Celiac Disease, Crohn's Disease or Chronic Ulcerative Colitis. While neoplasms such as malignant lymphoma have been reported in patients with celiac disease, carcinoids have rarely been found in association with the disease. One case has been reported of a carcinoid tumor in the gastric antrum of a patient with celiac disease (1) and another patient has been reported with atypical carcinoid tumor in the small bowel associated with celiac disease (2).

Carcinoid has been reported with concurrent Crohn's disease (3-7) and a few patients have been reported with a colonic carcinoid and ulcerative colitis (8,9).

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CARCINOID SYNDROME

This was the third syndrome described in which the secretion of a neurohumoral substance was the mediator of a disease (Table 10) (1). The other syndromes and the order in which they were described are shown also in Table 10.

Although carcinoid tumors were described over a 100 years ago, the clinical syndrome was not described in detail until 1954 by Waldenström and colleagues (4,11). In 1951, the case of a young man with vasomotor symptoms consisting of rapidly changing cyanotic patches and symptoms of valvular disease of the right side of the heart was reported (12). The patient died after an angiographic examination. The autopsy revealed pulmonary stenosis, tricuspid regurgitation and a small carcinoid of the ileum with extensive abdominal metastases. The classic paper published in 1954 described the syndrome in detail. The syndrome consists of carcinoids of the small intestine, metastases to the liver, and in several cases, metastases to other parenchymatous organs, valvular disease of the right side of the heart without septal defects, sudden flushing of the skin, an unusual type of patchy changing cyanosis, frequent watery stools, "asthma" and finally, edema and ascites. The cause of these findings was believed to be a malignant carcinoid of the small intestine with hormonal properties and extensive metastases to the liver. The authors believed that of the known vasoactive substances, 5-hydroxytryptamine (enteramine or serotonin) was the one which seemed most likely to correspond with the signs and symptoms of the syndrome. At the time of the publication in 1954, serotonin had recently been extracted in relatively large amounts from a carcinoid (13).

TABLE 10. HISTORICAL DESCRIPTION OF TUMORS PRODUCING NEUROHUMORAL AGENTS (FROM REF. 1).

YEAR	TUMOR	CELLS GIVING RISE TO TUMOR	PROMINENT NEUROHUMORAL SUBSTANCE	PROMINENT SYMPTOM
1927[2]	Insulinoma	Beta cell pancreas	Insulin	Hypoglycemia
1929[3]	Pheochromocytoma	Chromaffin cell adrenal medulla	Catecholamines	Hypertension
1954[4]	Carcinoid	Kulchitsky's cells	Serotonin	Facial flushing, diarrhea
1955[5]	Gastrinoma (Zollinger-Ellison syndrome)	Unknown cell pancreas	Gastrin	Peptic ulcer, diarrhea
1958[6]	Verner-Morrison syndrome	Unknown cell pancreas	Vasoactive intestinal peptide (VIP)	Watery diarrhea and hypokalemia
1970[7]	Medullary carcinoma thyroid	C cells thyroid	Calcitonin	Diarrhea
1974[8]	Glucagonoma	Alpha cells pancreas	Glucagon	Diabetes and skin eruptions
1977[9]	Somatostatinoma	Delta cells pancreas	Somatostatin	Diabetes and steatorrhea
1979[10]	PPoma	PP cells of pancreas	Pancreatic polypeptide	None

Most carcinoid tumors that are endocrinologically active but have not metastasized to the liver, function below the threshold level of clinical symptoms. The reason(s) for this are not known. One possible explanation is that the tumor cells have a low turnover rate for hormones and secrete only small quantities of active peptides. This is unlikely, especially with foregut carcinoids, because the tumor cells have a rapid turnover of hormones and the cells lack storage capacity. The absence of symptoms with some carcinoids may be related to the production of biologically inactive products such as prohormones or to rapid degradation of secreted agents in the tumor itself or blood stream (14). In tumors that produce neuropeptides, the lack of symptoms is probably due to the fact that the number of cells in the tumor is too small to cause peptide release that, in turn, would lead to symptoms (15). Because most carcinoids either produce or release only small amounts of biologically active substances, it is only after widespread metastases that sufficient quantities of active peptides or amines enter the bloodstream to cause symptoms and the carcinoid syndrome (15).

Pathophysiology of the Carcinoid Syndrome. One year prior to the description of the carcinoid syndrome, Lembeck had demonstrated serotonin in carcinoids (13). Thus, the whole spectrum of symptoms was believed related to production and secretion of serotonin (5-HT) by the tumor and its metastases. Through the years other biologically active peptides and amines have been isolated from patients with the carcinoid syndrome. However, serotonin and its metabolites remain the predominant contributors and markers of the disease.

The metabolic pathways for serotonin (5 HT) synthesis, degradation and urinary excretion in the most common or typical form of carcinoid cell is shown in Figure 5.

The rate limiting step in serotonin synthesis by carcinoid tumor cells in most patients is the conversion of tryptophan to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (1,2). Dopa-decarboxylase then rapidly converts 5-HTP to serotonin (5-HT). Serotonin is then stored in secretory granules or is secreted into the vascular compartment where most is taken up by platelets and stored in secretory granules. The remainder is free in the plasma and is con-

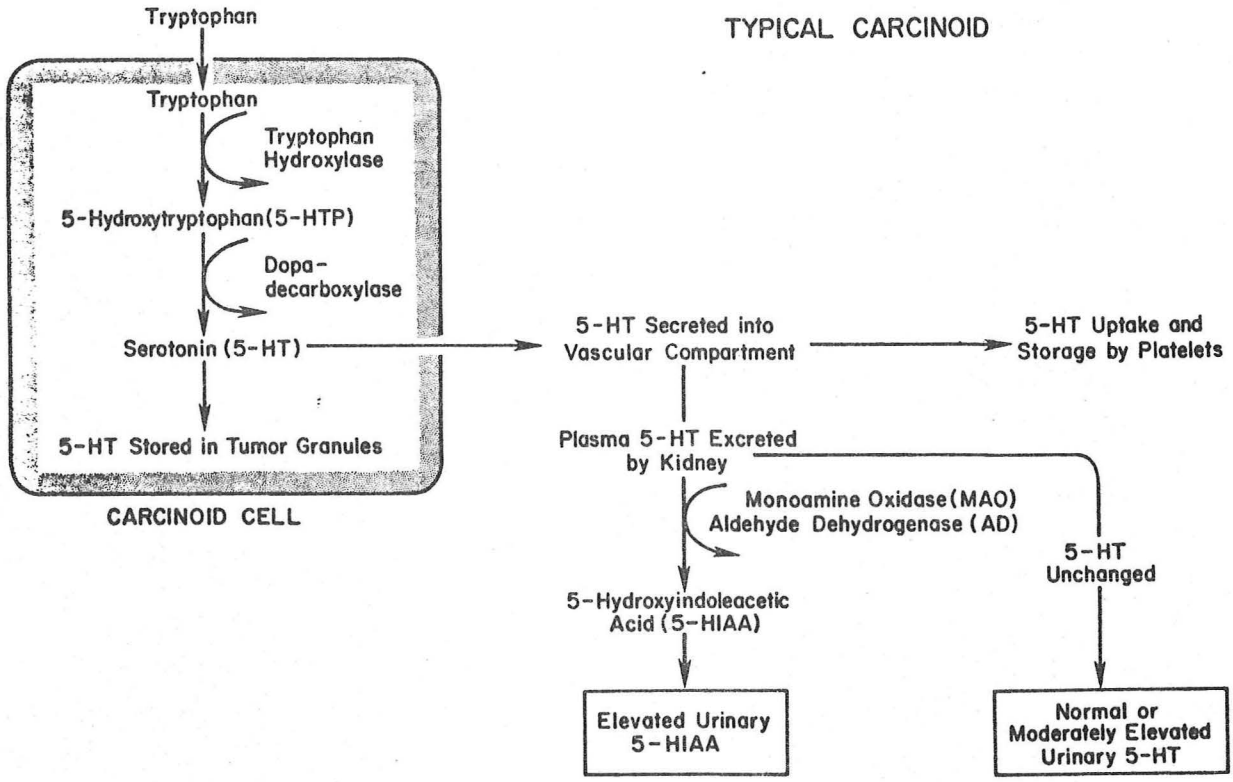

Figure 5. Metabolic pathways for synthesis, metabolism and excretion of serotonin in a typical carcinoid cell (adapted from Feldman, JM).

verted to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase and aldehyde dehydrogenase. Most of the circulating 5-HT is converted to 5-HIAA, thus leading to the high urinary levels of 5-HIAA in patients with carcinoid syndrome. The amount of urinary 5-HT is usually normal or only moderately elevated.

A few patients have carcinoid cells that contain an atypical metabolic pathway as illustrated in Figure 6. Most patients who have tumors with this pathway are those with foregut carcinoids and patients with carcinoids of the bronchus (see Table 4).

In these patients, 5-HT cannot be effectively produced and stored in tumor granules (18). This is thought to be secondary to a deficiency of dopa-decarboxylase. Thus, only a small amount of 5-HT is secreted into the vascular compartment. Most of the 5-HTP that is released from this type of carcinoid is decarboxylated to 5-HT in extrarenal sites. Then, 5-HT is oxidized by monamine oxidase and aldehyde dehydrogenase and is excreted by the kidneys and appears in the urine as 5-HIAA (16). Some 5-HTP escapes decarboxylation while other 5-HT escapes oxidation. Thus, some 5-HTP and 5-HT are excreted into the urine as 5-HTP and 5-HT. The levels of 5-HTP and 5-HT can be markedly increased in the urine in a few patients while 5-HIAA is only moderately elevated.

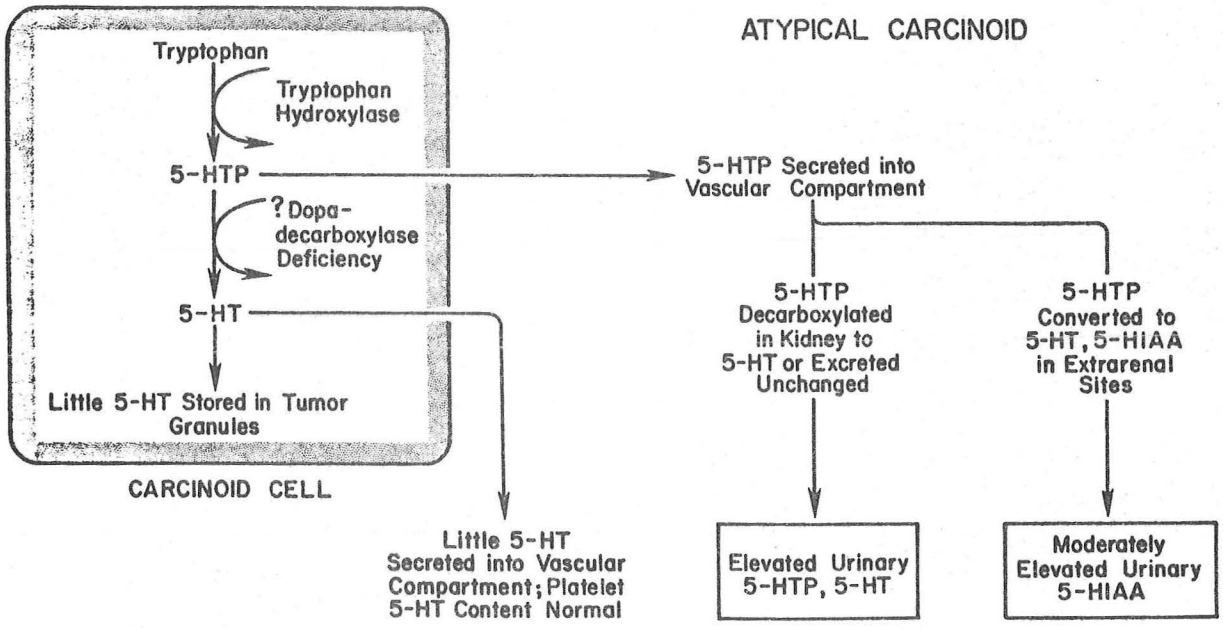

FIGURE 6. Metabolic pathways for synthesis, metabolism and excretion of serotonin in an atypical carcinoid cell (adapted from Feldman, JM).

It is now recognized that only part of the carcinoid syndrome can be related to increased serotonin levels (15). Some of the substances believed responsible for the syndrome as well as the symptoms produced are listed in Table 11. Other neuropeptides and amines also may be involved in causing some of the signs and symptoms. Serotonin may be responsible for diarrhea since tone and motility of the human jejunum and fluid secretion can be increased by serotonin infusions (19,20) and diarrhea can be treated with serotonin antagonists such as methysergide (21), cyprohepatadine (22) and ketanserin (23) (see diarrhea below). These serotonin antagonists do not alter flushing. Thus, it seems unlikely that flushing is related to increased serotonin secretion (21) (see below).

TABLE 11. MEDIATORS OF THE CARCINOID SYNDROME AND THE SIGNS AND SYMPTOMS PRODUCED

POSSIBLE MEDIATORS	SIGNS AND SYMPTOMS
Serotonin	Diarrhea (intestinal hypermotility and hypersecretion) Fibrosis Bronchoconstriction Edema
Kallikrein (bradykinin)	Vasodilatation (flushing?)
Tachykinins (Substance P, neurokinin A, neuropeptide K)	Vasodilatation (flushing?)
Prostaglandins	Diarrhea? Flushing?

Adapted from Ref. 1

Signs and Symptoms of the Carcinoid Syndrome. Symptoms in 138 patients with the carcinoid syndrome are summarized in Table 12 (24).

TABLE 12. PERCENT OF VARIOUS SYMPTOMS IN 138 PATIENTS WITH CARCINOID SYNDROME[a]

ORGAN	SYMPTOM	PERCENT OF PATIENTS WITH EACH SYMPTOM
Skin	Flushing	94
	Telangiectasia	25
	Cyanosis	18
	Pellagra	7
Gastrointestinal tract	Diarrhea	78
	Cramping	51
Heart	Valvular lesions	
	Right heart	40
	Left heart	13
Respiratory tract	Bronchoconstriction (wheezing)	19
Renal	Peripheral edema	19
Joints	Arthritis	7

a Table from Ref. 15; data from Ref. 24.

The major symptoms are flushing, diarrhea, abdominal pain and cardiac lesions. These are followed by asthma and edema. Abdominal pain can occur as a result of small bowel obstruction or intussusception (see section on small intestinal carcinoids) but it also can occur in patients with carcinoid syndrome and non-intestinal tumors. The cause of pain in these patients is unclear.

Flushing. This can be episodic or permanent and is the major manifestation of the syndrome. Initially, it was thought that the carcinoid flush resulted from serotonin release which was known to have pharmacological vascular effects (13). It later became evident that serotonin either was not the cause or certainly was not the only cause of flushing (25). The episodes are frequently provoked by an emotional stimulus, food, oral and intravenous ethanol and various pharmacologic stimuli such as pentagastrin, adrenaline and noradrenaline, isoproterenol and calcium salts.

There are at least four types of flush (26):

1) In this type, a diffuse erythematous flush occurs which affects mainly the face, neck and upper anterior chest, but frequently spreads over the skin of the back and affects the abdomen and palms. This type usually occurs in paroxysms which are short and last a few minutes. Patients usually appear normal between flushes.

2) The second type has a violatious tinge which affects the same areas of the body but lasts longer. Patients with this type often have an extremely elevated urinary 5-HIAA output.

3) The third type is usually associated with bronchial carcinoids. These flushes often last several hours and even days. The skin becomes red and frequently slightly purplish and areas of the body other than the usual flushing areas are involved. Lacrimation occurs and the conjunctiva are suffused.

4) This type of flush is bright red and patchy. The red flush is an especially vivid red and the red patches are intermingled between patches that are brightly white. This type of flushing seems to be associated with gastric carcinoids and increased histamine production.

The fact that, clinically, there appear to be at least four types of flushes suggests that different substances alone, or in concert, affect different parts of the vascular bed of the skin. One group of investigators showed that serotonin could not be the sole substance responsible for flushing since serotonin did not produce a true carcinoid flush when given intravenously (27). Kallikrein was suggested as the carcinoid flushing substance by Oates and colleagues (28). Furthermore, they found that the hepatic venous blood draining carcinoid liver metastases contained a bradykinin-like substance during an induced flush. When bradykinin was measured in arterial blood during a provoked carcinoid flush, the concentrations of bradykinin increased. However, plasma bradykinin did not increase during flushing in all patients and intravenous bradykinin did not qualitatively reproduce the spontaneous flush. A recent series of experiments by Gustafsen and co-workers also suggest that bradykinin is not the cause of carcinoid flush (29).

There are a number of potential flushing substances that can be found in carcinoid tumors. These include histamine (especially from gastric carcinoids),

substance P, prostaglandins and various tachykinins. Neuropeptide K has been found in plasma and tumors from patients with the carcinoid syndrome (30) and radioimmunoassay techniques and chromographic separation have identified neuropeptide K as a valid candidate for the cause of flushing. This, however, has not been established with certainty. When substance P is given intravenously to humans, it produces flushing but whether the level of substance P found in patients with carcinoid syndrome is similar to the levels associated with intravenous doses is not known. It also is not known whether neurokinin A or neuropeptide K causes flushing in humans. Basal levels of substance P and neurokinin A are increased in some patients with the carcinoid syndrome but a relationship between this increase and the degree of flush has not been established (see section on Treatment for Carcinoid Syndrome).

Diarrhea. The second most common manifestation of carcinoid syndrome is recurrent episodes of mild to explosive diarrhea. Diarrhea is frequently associated with abdominal pain and may or may not be associated with episodes of flushing. Patients may have only a slight increase in frequency of stools but may have as many as 20 bowel movements daily (31). The cause(s) of diarrhea presently are unclear although there are several possible explanations. Serotonin seems to be a likely candidate either by causing intestinal secretion or by causing an effect on gastrointestinal motility (32,33). The fact that somatostatin increased water and electrolyte absorption (34) and decreased diarrhea (35) while causing a decrease in urinary 5-HIAA levels also supports serotonin as a possible cause of diarrhea. Other possible mediators include calcitonin, glucagon, gastrin, vasoactive intestinal peptide, and prostaglandins.

Carcinoid Crisis. This is one of the most dramatic manifestations of the carcinoid syndrome (36). Usually, this occurs in patients who have markedly elevated 5-HIAA levels and may occur more frequently in patients with a foregut carcinoid. Crisis may develop spontaneously but is frequently precipitated by physically stressful situations, induction of anesthesia (37,38) or following a course of chemotherapy. Carcinoid crisis is frequently accompanied by a generalized flush. Diarrhea and abdominal pain may develop and central nervous system abnormalities ranging from light headedness through somnolence to deep coma may occur. Patients also may develop tachycardia, rhythm irregularity, hypertension or severe hypotension (see Treatment of Carcinoid Syndrome with Somatostatin Analog).

Carcinoid Heart Disease. Carcinoid heart disease causes predominately right-sided valvular abnormalities (39). It is believed that hepatic metastases from carcinoid tumors release vasoactive substances that chronically bathe and damage the tricuspid and pulmonary valves. These substances appear to be inactivated by the liver. Thus, liver metastases are a prerequisite for cardiac involvement (39). An exception to this rule appears to be ovarian carcinoids, since both ovaries drain directly into the inferior vena cava and bypass the liver.

Carcinoid heart disease consists usually of a grossly visible, focal, uniform fibrous lesion on the mural endocardium of the right atrium, right ventricle, and sometimes on the left ventricle. The disease includes the presence of diffuse or focal thickening of the tricuspid cusps and/or pulmonic valves with or without involvement of the mitral and/or aortic valves.

In one autopsy study of 21 patients (57%) with carcinoid heart disease and 15 patients (43%) without carcinoid heart disease (40), there were no signifi-

cant differences in sex, mean age or other symptoms attributable to carcinoid syndrome. The average length of illness was 1.6 years shorter for the group with carcinoid heart disease compared with the group without carcinoid heart disease. The range of survival from onset of symptoms to death in the group with heart disease was 0.5 to 13 years while the range of survival from the onset of symptoms to death in the group without heart disease was 1 to 25 years. There was no significant difference in the level of 5-HIAA in the urine between those with and without heart disease although the two groups differed in the site of the primary tumor (40). The small intestine was the site of the carcinoid in 95% of patients with heart disease while it was the site of the primary tumor in only 67% of those without heart disease ($P < 0.05$).

Other findings that were increased in patients with carcinoid heart disease included a higher incidence of wheezing, peritoneal effusions, increased cardiothoracic ratios of greater than 0.5 and a higher incidence of low voltage on electrocardiogram. The cause of death appeared to be the result of heart disease in 9 of the 21 patients with carcinoid heart disease and in none of the 15 without heart disease.

Why carcinoid heart disease occurs in some patients with the carcinoid syndrome and not in others is not known (40). It has been stated that patients with heart disease secondary to carcinoid syndrome have higher blood serotonin levels than in those without heart disease. This, however, was not true in the group of patients discussed above (40).

Carcinoid heart disease is a unique form of cardiac disease in that it consists of the deposition of an unusual type of fibrous tissue that is devoid of elastic fibrils. The fibrous tissue contains smooth muscle cells and mucopolysaccharide material. This substance deposits on the mural and valvular endocardium, primarily on the right side of the heart (40,41).

An interesting feature of the carcinoid plaques is that by histologic and electron microscopic appearance they all look alike. In other words they do not appear to go through any developmental stages. This suggests that the endocardial plaques result from substances originating from the blood. On electron microscopy the carcinoid plaques are composed of a material which is consistent with the appearance of young collagen (39).

The plaques are much more common on the right side of the heart than on the left (40). If lesions do occur on the left, the plaques on the right are always more extensive and larger. Most patients have involvement of both tricuspid and pulmonic valves. Many patients with carcinoid heart disease have carcinoid plaques on the mural endocardium of the right atrium and right ventricle.

The functional consequences of carcinoid plaques on the tricuspid and pulmonic valves are quite different even though the composition and location of the plaques are similar (40). The plaques occur almost entirely on the downstream side of the valvular leaflets, that is on the valvular aspects of the septal and posterior tricuspid leaflets and on the pulmonary arterial side of the pulmonic valve cusps. The results of the downstream deposition of the plaques is for the leaflet to adhere to the underlying mural endocardium or to the underlying pulmonary arterial endothelium via the carcinoid plaques (40). The fibrous tissue serves as a constricting substance such that the "ring" of both right-sided cardiac valves is made smaller than normal and at the same time leaflet mobility is decreased. This results in tricuspid regurgitation with or without some degree of stenosis. Most patients with carcinoid heart disease have a much greater degree of tricuspid regurgitation than stenosis.

Stenosis is the major pulmonic valve lesion (40) although all patients with pulmonary stenosis have some degree of regurgitation. Carcinoid syndrome is said to be the only cardiac disease in which both right-sided valves are frequently involved simultaneously (40). The most common functional results of right-sided carcinoid heart disease are pulmonic stenosis and tricuspid regurgitation.

The diagnosis of carcinoid heart disease usually can be made by noninvasive methods. Two dimensional echocardiography has been used to evaluate patients with carcinoid heart disease (39). With echocardiography, the tricuspid valve is usually easier to evaluate than the pulmonic valve. Also, two-dimensional echocardiography has been suggested as a method of following the progression of valvular heart disease and a method that might assist in formulating medical therapy. It also might help in identifying those patients who would benefit from tricuspid valve replacement (41).

Patients with carcinoid heart disease usually follow a course that leads to eventual development and later worsening of heart failure (17). Patients may acquire severe symptoms and eventually die from cardiac decompensation. Valve replacement may be required and in some patients surgery is successful in relieving symptoms (42-46).

Diagnosis of the Carcinoid Syndrome. The diagnosis is based usually on an increased level of 5-HIAA in the urine. Some authors have quoted a level of 5-HIAA above 10 mg per 24 h as abnormal. However, according to data shown in Table 13, values for urinary excretion of 5-HIAA in patients with carcinoid syndrome ranged from 23-1632 mg/24 h.

TABLE 13. SEROTONIN AND ITS METABOLITES IN PATIENTS WITH CARCINOID TUMORS AND THE CARCINOID SYNDROME (DATA FROM REF. 16)

	URINARY EXCRETION			SERUM
	5-HIAA mg/24h	5-HT µg/24h	5-HTP µg/24h	5-HT µg/ml
NORMAL SUBJECTS				
(MEAN)	4.1	133	<50	0.14
(RANGE)	(2.5-8.7)	(40-250)		(0.01-0.35)
PATIENTS				
(MEAN)	305	681	663	1.79
(RANGE)	(23-1632)	(130-2596)	(20-327)	(0.29-4.18)

During the period of urine collection all serotonin-containing foods such as walnuts, pecans, butternuts, bananas, pineapples and tomatoes and drugs such as phenothiazines should be avoided since these foods and drugs can cause spurious but mild increases in 5-HIAA excretion.

Pentagastrin Test in Carcinoid Syndrome. Several agents have been used to provoke symptoms in patients to establish the diagnosis of carcinoid syndrome.

These include alcohol, catecholamines, calcium, and pentagastrin (47). In one series of 17 patients with midgut carcinoids, 16 patients with metastatic disease developed a moderate decrease in blood pressure which was associated with flushing and/or gastrointestinal symptoms within 3 min after injection of pentagastrin (0.6 µg/kg). The signs and symptoms which developed correlated with an increase in peripheral serotonin levels.

In another series of experiments the levels of serotonin and substance P were assayed in the peripheral blood of 17 patients with known mid-gut carcinoids, 16 of whom had hepatic metastases (23). All patients had elevated levels of serotonin and substance P. Pentagastrin caused flushing in all patients, induced gastrointestinal symptoms in all but one of the patients with hepatic metastasis and caused an increase in circulating 5-HT level.

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TREATMENT OF CARCINOID TUMORS AND THE MALIGNANT CARCINOID SYNDROME.

Most localized carcinoid tumors are found at the time of appendectomy or at a proctoscopic examination performed for some reason other than to locate a carcinoid tumor. At the time of discovery, the method of treatment is determined usually by the size of the tumor. Most (approximately 70-90%) will be very small (< 1 cm in diameter) (1). Conservative local removal either by appendectomy or fulguration of a rectal lesion is all that is required. When fulguration or local excision of a small rectal carcinoid (equal to or < 1 cm) was performed or a simple appendectomy (all lesions < 1.9 cm in diameter and 72% < 1.0 cm) was carried out, there were no recurrences at up to 10 years (3,4). Thus, cure rates are relatively high and the major risk is from the performance of too radical a surgical procedure. The patient should be reassured and follow-up procedures including measurement of urine 5-hydroxyindoleacetic acid should not be necessary (1).

In contrast, primary tumors of the gastrointestinal tract measuring 2 cm or larger have a strong propensity (80% or more) to metastasize. These tumors should be treated by aggressive cancer operations: right hemicolectomy for appendiceal lesions and anterior or anterior-posterior-resections for rectal tumors (1). Patients should be told that compared to other malignancies, carcinoids have a relative good prognosis even if metastases are present (5). The average duration of disease from onset of symptoms to death with metastasis is 8.6 years, with a range of 6 months to 29 years.

The method of treating patients with tumors measuring 1-2 cm in diameter, where approximately 50% of the patients will have either regional, nodal or distant metastasis is more controversial (1). In some of these patients, metastasis will not be present at the time of examination. For patients with what appears to be localized disease, clinical judgement must be based on actual size of the tumor, degree of local invasion, necessity for anterior-posterior versus anterior resection for rectal lesions, age of the patient and estimated operative surgical risk (1) (see sections on Carcinoids of Appendix and Rectum).

Most intestinal carcinoids are so small in size and arise so deep in the mucosa that they rarely disturb normal physiology and rarely cause clinical symptoms (1). A symptomatic tumor has almost always invaded the mesentery and frequently has metastasized at least to regional lymph nodes. Localized disease is usually an incidental finding at necropsy or, less commonly, at surgery performed for other purposes. Similar to rectal and appendiceal tumors, these localized carcinoids are frequently less than one centimeter in diameter. Local excision usually is recommended for lesions < 1 cm in diameter whereas wider segmental dissection of the mesentery is recommended for tumors 1 cm or greater in diameter (1).

In another series, surgical therapy was performed for small intestinal carcinoids in 66 patients (6). Only three patients had tumors that could be removed by local excision. All of these patients were alive at follow-up (mean, 4.3 years). Twenty-nine patients had a small bowel resection with removal of lymph node bearing mesentery and 16 patients had a right hemicolectomy. A palliative procedure and bypass was the only operation that could be performed in 18 patients. Only 17 of the 29 patients with small bowel and lymph node resection, 10 of the 16 patients with right hemicolectomy, and 1 of the 18 patients with a palliative procedure were alive at follow-up. Thus, while survival in patients with small bowel carcinoids and local metastases may be better than that in patients with adenocarcinoma, the overall mean survival was only 4.3 years.

Carcinoids of the stomach and small bowel frequently are multicentric. In one study, 29% of 207 patients had more than one primary lesion (4) while in a review, 7% of 90 patients had multiple gastric carcinoids (7). Gastric carcinoids frequently are close together so that if the decision is made to remove the tumors, several can be resected simultaneously. When there are multiple gastric carcinoids, partial gastric resection may be indicated to include most of the larger gastric carcinoids within the surgical resection. Total gastrectomies have been performed in some patients but may not be essential. If the hypothesis is correct (see ECL hyperplasia and gastric carcinoids) that hypergastrinemia is the cause for some gastric carcinoids, an antrectomy might be considered sufficient therapy in some patients. By doing this procedure, gastrin, the presumed stimulant of ECL hyperplasia and gastric carcinoids, is removed. If there are extensive small bowel carcinoids, segmental small bowel resection should be performed to include the largest of the carcinoid tumors. Tumors < 1 cm in diameter probably should not be removed.

Treatment of Carcinoid Tumors with Regional Lymph Node Involvement.

Carcinoid tumors that have spread to regional lymph nodes should be treated with aggressive cancer therapy. Treating carcinoid tumors that have spread to regional lymph nodes should be viewed differently than treating patients with gastric or colorectal adenocarcinoma. Resection of remote lymph nodes in patients with carcinoid tumors usually will produce a high frequency of cures or long-term survival whereas such success is uncommon in most other forms of cancer. If regional lymph nodes cannot be resected, major surgical efforts to debulk tumor probably are not justified (1). Radiation therapy has been attempted occasionally for locally unresectable carcinoid tumors. Regression of the tumor (8) and reasonably long patient survival have been reported, especially when compared with other forms of cancer.

Therapy of Metastatic Carcinoid Tumors.

Chemotherapy. Biologic behavior of metastatic endocrine tumors including carcinoids is variable. Frequently, chemotherapy is not indicated even though metastatic disease is present. For example, aggressive chemotherapy should not be used in patients with metastatic carcinoid tumors if they do not have symp-

toms referable to the tumor or if only minor symptoms secondary to the carcinoid syndrome are present (9). If symptoms are severe enough to interfere with daily activities, chemotherapy should be considered. Another indication for chemotherapy is the development of carcinoid heart disease and an excretion of 5-HIAA of more than 150 mg per 24 hours (1). One reason for withholding chemotherapy as long as possible is the fact that the clinical benefit is relatively low yet the unwarranted toxicity relatively high.

Another problem associated with chemotherapy of carcinoids has been the lack of consistent definition of a response to therapy (9). The presence of a tumor product in serum or urine has allowed investigators to detect reductions in secretion of these substances without necessarily observing objective regression of tumor masses. Frequently, these decreases in tumor products are associated with symptomatic improvement and thus, are important guides to the response to therapy. In the past, many chemotherapeutic trials did not have definite response criteria and any decrease in tumor size or decline in tumor secretion was interpreted as a response to chemotherapy. However, this may or may not have been correct. Currently, serum levels of most hormones can be measured to determine the pattern of tumor secretion and to define a response to therapy. With the current emphasis on biochemical markers of disease activity, a 50% or greater decrease in the serum or urine hormone level secreted by a particular tumor, is frequently considered a therapeutic response whether or not there has been a decrease in size of measurable tumor. For example, a decrease in urinary 5-HIAA of >50% is considered at least at that point in time a therapeutic success.

Most patients that have been treated by protocol have been treated in Phase II trials. In these trials, the studies are designed to determine the effectiveness of an agent in a specific human tumor (in this case, a metastatic carcinoid), to assess dose-response relationships, and to further delineate toxicity in relationship to therapeutic effects.

Single-agent chemotherapeutic regimens for carcinoid tumors are summarized in Table 14.

TABLE 14. SINGLE-AGENT CHEMOTHERAPY FOR CARCINOID TUMORS (FROM REF. 9)

AGENT	PATIENTS	DOSE OF DRUG	OBJECTIVE RESPONSE NUMBER (PERCENT)	REF.
Doxorubicin	33	60 mg/m² every 3 to 4 weeks	7 (21)	(1)
5-Fluorouracil	19	500 mg/m² per day in 5-day courses given every 5 weeks	5 (26)	(1)
Dacarbazine	15	Dosage not given	2 (13)	(10)
Actinomycin D	17	Dosage not given	1 (6)	(10)
Cisplatin	15	45 to 90 mg/m² by rapid IV infusion, repeated every 3 to 4 weeks	1 (7)	(11)
Streptozotocin	6	Dosage not given	1 (17)	(1)

None of the single-agent chemotherapeutic drugs have been very successful in treating patients with carcinoid syndrome. Although only slightly better than doxorubicin, the initial reports by Moertel (3) indicated that 5-fluorouracil in a dose of 500 mg/m² day in five-day courses every five weeks gave the best objective responses. There are several other reports in which a few patients responded to one or another of the drugs. For example, in one report two of 15 patients responded partially to dacarbazine (10).

Streptozotocin-based combination chemotherapy has been used to treat a number of neuroendocrine tumors including metastatic carcinoids. Some of the combinations of streptozotocin plus other agents are listed in Table 15.

TABLE 15. STREPTOZOTOCIN-BASED COMBINATION CHEMOTHERAPY REGIMENS FOR CARCINOID TUMORS (FROM REF. 9)

REGIMEN	PATIENT	OBJECTIVE RESPONSE NUMBER (PERCENT)	REFERENCE
Streptozotocin* plus 5-fluorouracil	43	14 (33)	(1)
Streptozotocin plus cyclophosphamide	47	12 (26)	(12)
Streptozotocin† plus 5-fluorouracil	80	18 (23)	(13)
5-Fluorouracil plus doxorubicin plus cyclophosphamide plus streptozotocin	20	7 (35)	(14)
Streptozotocin (weekly) plus doxorubicin	10	4 (40)	(15)

* Streptozotocin in five-day courses repeated every six weeks.
† Streptozotocin in five-day courses repeated every 10 weeks.

None of the regimens listed in Table 15 appear to offer any clear-cut advantage over any of the other regimens. Even the four-drug regimen comprised of 5-fluorouracil, streptozotocin, doxorubicin and cyclophosphamide did not appear to offer any clear-cut therapeutic advantage over any of the other drug combinations. It appeared that the response was slightly better with streptozotocin and 5-fluorouracil but the differences were not statistically significant. Also, the response rate was significantly better for small bowel carcinoids than for carcinoids of pulmonary or unknown origin.

Non-chemotherapeutic Agents. These also have been reported to produce tumor regression in patients with carcinoid syndrome. For example, reduced tumor size has been reported with cyproheptadine but this observation needs to be confirmed

(16). Leukocyte interferon also has been used with some success in 6 patients with carcinoid syndrome (17). A total of 9 patients, 6 of whom had carcinoid syndrome were treated. Treatment with interferon ameliorated the manifestations of the carcinoid syndrome and led to prompt and continuing decreases in urinary levels of 5-HIAA. Also, serum levels of human chorionic/gonadotropin subunits and pancreatic polypeptide were reduced in all 6 patients with liver metastases but interferon had no effect in two of three patients with only lymph-node involvement. Unfortunately, after the treatment period, 5 of the 6 responders had relapses in clinical manifestations and increases in hormone levels. While results of this study created interest in interferon as a therapeutic modality, the results need to be confirmed.

Hepatic Artery Ligation. This has been performed at the time of laparotomy and has been used to treat a few patients with carcinoid syndrome (18). In this study, 6 patients were treated by hepatic artery ligation and facial flushing ceased and diarrhea was reduced in all patients. Unfortunately, the duration of response was short and ranged from only 3 to 10 months (median, 5 months). Other workers have shown that hepatic artery occlusion by embolization is an effective means of inducing tumor debulking in carcinoid syndrome (19-21) (see below). In patients treated with hepatic artery occlusion there have been transient abnormalities in liver function tests. However, since the occlusion-induced dysfunction has been transient, the vascular occlusion does not interfere with future chemotherapy (9).

Early results of a trial of sequential hepatic artery occlusion and chemotherapy for metastatic carcinoid tumor have been reported (22). Ten symptomatic patients with proven hepatic metastases were treated with hepatic artery occlusion either by surgical or percutaneous embolization. Three weeks later, therapy was initiated with dacarbazine, 250 mg/m^2 for 5 days, plus doxorubicin, 60 mg/m^2 intravenously alternating every four weeks with 5-fluorouracil, 400 mg/m^2 for 5 days plus streptozotocin, 500 mg/m^2 for 5 days. Nine of the 10 patients had dramatic or complete relief of symptoms. The 5-HIAA level which was increased prior to therapy was reduced by 60-100% after treatment. The tenth patient had minor improvement for 12 months (9). Abnormal liver function tests occurred with hepatic artery occlusion and side effects from chemotherapy developed. However, early results with this therapeutic program appear to provide better or more consistent results than either hepatic artery occlusion alone or chemotherapy alone.

Hepatic Artery Embolization. Some physicians recommend performing a cholecystectomy prior to the embolization. In one study, 18 patients with metastatic carcinoids were treated with gelfoam or polyvinyl alcohol foam for control of the carcinoid syndrome (21). Seventeen of the 18 patients showed clinical improvement including reduced skin flushing, diarrhea and bronchospasm. Fourteen patients demonstrated improvement in biochemical markers such as decreased urinary 5-HIAA levels. In another report, 25 patients with malignant carcinoid syndrome underwent hepatic artery embolization to palliate the symptoms of this syndrome. Twenty-three of the 25 patients could be evaluated: 20 patients responded to embolization with a median duration of response of approximately 11 months (23). Two patients died from complications of the procedure. Eighteen of the remaining 23 patients were evaluated as to effect on hepatic metastases and 5-HIAA. There was a reduction in the size of the hepatic metastases in 17 of the 18 patients and a decrease by 41% of pretreatment levels in the urine 5-HIAA values. While the authors of this paper state that hepatic artery

embolization provides the most effective treatment for carcinoid syndrome with hepatic metastases, other studies need to be performed before the true value of hepatic artery embolization can be evaluated adequately.

5-hydroxytryptamine (5-HT) Receptor Antagonists. Peripheral 5-hydroxytryptamine receptors have been divided into three groups: The D receptors (5 HT_2) which are present primarily on smooth muscle cells and the M receptors (5 HT_3) which are primarily neuronal and act by modulating the release of other neurotransmitters (24). The third 5 HT receptor is the 5 HT_1-like receptor. Remission of symptoms in carcinoid syndrome has been reported using a new 5-hydroxytryptamine M (5 HT_3) receptor antagonist (25). Several antagonists of the D (5 HT_2) (smooth muscle) receptors (e.g., methysergide) have been developed, and these have proved either poorly effective in the carcinoid syndrome or have relatively severe toxic effects (26). Diarrhea in three patients with the carcinoid syndrome was controlled by a new drug, ICS 205-930, suggesting that M receptors (5 HT_3) may mediate the secretory diarrhea of the carcinoid syndrome and also suggest that blockade of these receptors may play an important role in the symptomatic treatment of watery diarrhea in the carcinoid syndrome.

Other Treatment Approaches

Parachlorophenylalanine. This compound has been shown to relieve diarrhea and to reduce urinary 5-HIAA excretion but flushing is rarely reduced by this drug. Side effects such as hypersensitivity reactions and psychiatric disturbances, make it difficult to use long term (27).

Cyproheptadine. One group (16) reported regression of a carcinoid tumor in a patient treated with cyproheptadine. They hypothesized that this drug might affect tumor growth by blocking the effects of amines. A phase II study is underway currently at Mayo Clinic to evaluate the anti-tumor effect of this drug in patients with measurable disease (5).

Tamoxifen. This synthetic anti-estrogen was reported by investigators from Greece to cause symptomatic improvement in a patient with the carcinoid syndrome (28). A second report using this same drug also indicated objective tumor regression and biochemical improvement in that 5-HIAA excretion decreased from 174 to 15 mg/24 hours (29). A collaborative trial was carried out by the Mayo Clinic and the American Oncologic Hospital. Sixteen patients were treated with the compound and none showed evidence of objective improvement in malignant disease as measured by a reduction in tumor size or by a decrease in 5-HIAA levels (30).

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THERAPY OF CARCINOID SYNDROME WITH A SOMATOSTATIN ANALOGUE

The use of somatostatin in the management of hormone secreting tumors was proposed as early as 1974 (1-3). In that year the polypeptide growth-hormone release-inhibiting hormone (G.H.-R.I.H. or somatostatin) was shown to be a potent inhibitor of growth-hormone release and also to block thyroid-stimulating-hormone release factor (1). Later, many other studies were carried out demonstrating multiple effects of somatostatin on the pituitary and pancreatic cells and on the gastrointestinal tract. For example, somatostatin inhibits release of many peptides of the gastroenteropancreatic system, reduces gastric secretion, decreases exocrine pancreatic secretion and gallbladder contraction and reduces intestinal absorption (4). Until recently, natural somatostatin 14 was the only molecular form of somatostatin available and its

inhibitory activity towards both endocrine and exocrine gastroenteropancreatic secretions were well documented. The clinical benefits of somatostatin, however, were limited because of the relatively insurmountable problems of short duration of action of the compound. Several synthetic molecular forms of D amino-acid substitutes also had short-term activity (a few minutes after a single injection) and only prolonged infusion of somatostatin allowed meaningful therapeutic results to be obtained. In spite of the short duration of effect, native somatostatin was reported to be effective in blocking the carcinoid flush induced by pentagastrin, reducing circulating levels of serotonin and controlling other symptoms associated with the carcinoid syndrome as long as native somatostatin was infused (5,6). Unfortunately, the agent had limited therapeutic application because of its short half-life.

To circumvent the short duration of effect and the necessity for giving somatostatin by continuous intravenous infusion, an analogue of somatostatin was developed. This analogue (octreotide, SMS 201-995, Sandostatin) has been used in treating a number of signs and symptoms related to various endocrine tumors. The structure of the synthetic octapeptide of somatostatin is shown in Figure 7.

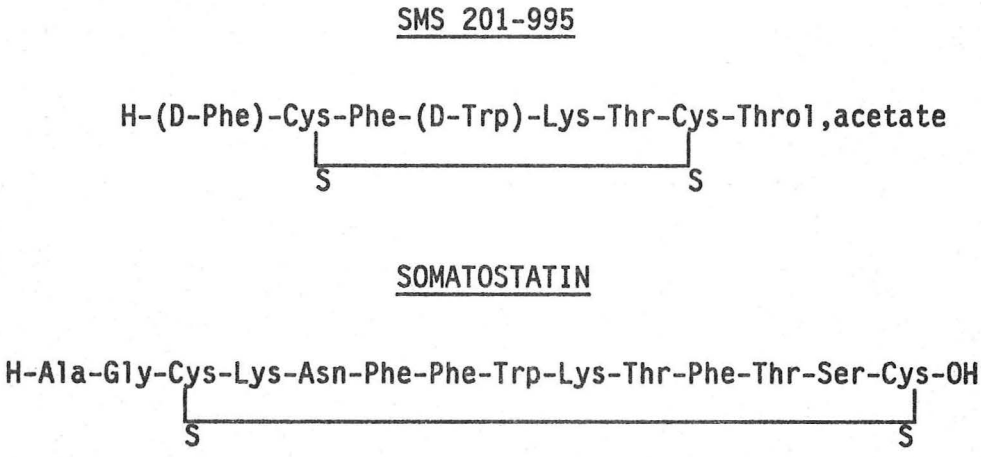

Figure 7. Amino acid sequence of somatostatin analogue (octreotide, SMS 201-995), top, and natural somastostatin, bottom.

The somatostatin analogue is completely and relatively rapidly absorbed after subcutaneous administration in dogs, rhesus monkeys and humans (7). Reports indicate that after subcutaneous injection of 50-100 µg to normal volunteers, peak plasma levels occur between 15 and 30 minutes and perhaps even up to one hour later. Oral absorption of somatostatin analogue is poor, with only 1-3% of a dose being absorbed.

Somatostatin analogue has been effective in treating a variety of disorders resistant to standard therapies including acromegaly (8,9), Zollinger-Ellison syndrome (10,11), hypoglycemia, pancreatic ascites, and cholera (12,13). In treating acromegaly, somatostatin analogue has produced a prolonged reduction in the level of growth hormone secretion and in many instances shrinkage of pituitary masses and improvement in neurological symptoms (14,15). Therapy with somatostatin analogue appears effective in treating certain forms of diarrhea including those associated with ileostomy and pancreatic cholera syndromes (13,16,17).

Somatostatin analogue also has been used to treat a number of gastrointestinal neoplasms of islet cell origin including insulinoma, somatostatinoma, gastrinoma, tumors resulting from hypersecretion of vasoactive intestinal peptide, glucagonoma and multiple endocrine neoplasms (18-23). In addition, as will be discussed in more detail below, the analogue has remarkable ability to relieve symptoms due to the vasopressor release of carcinoid tumors (24,25).

Somatostatin decreases the stool output in diarrhea associated with tumors secreting vasoactive intestinal polypeptide (VIP) and the carcinoid syndrome (26-29). In these studies, a reduction of 5-HIAA excretion has been found as has a decrease in circulating levels of other hormones. This decrease is unlikely to be the only mechanism of action of somatostatin since reduced plasma concentrations of these secretagogues frequently remain in the range associated with diarrhea in normal volunteers challenged with these agents (29) and found in many patients with the pancreatic cholera syndrome (30).

Somatostatin analogue is administered usually in a dose of 50-150 µg two to three times daily. When given in this regimen, it has been effective in reducing symptoms in most patients with the carcinoid syndrome (31). The somatostatin analogue has been evaluated at the Mayo Clinic using two separate protocols in 54 patients (24,32). Results in the first 25 patients are shown in Table 16.

TABLE 16. RESULTS OF THERAPY OF THE MALIGNANT CARCINOID SYNDROME WITH SOMATOSTATIN ANALOGUE (FROM REF. 33)

FEATURE	NO. OF TREATMENT PATIENTS	BEST RESPONSE >50% DECREASE	BEST RESPONSE MINOR RESPONSE	BEST RESPONSE NO RESPONSE	MONTHS OF MEDIAN (RANGE)
		no. of patients			
Flushing	24	19	3	2	12(2-18)
Diarrhea	25	19	3	3	12(3-18)
Urinary excretion of 5-HIAA	25	18	6	1	12(1-18)

In these patients, the dosage was 50 µg twice daily on day 1, 100 µg twice daily on day 2 and 150 µg three times daily, thereafter. Flushing and diarrhea was decreased by >50% in 19 patients and some response was noted in another 3 patients. In 18 of the 25 patients (72%), a 50% or greater decrease in 5-HIAA level occurred after therapy. In some patients, there was resolution of hepatic pain, improvement in liver function tests and regression of tumor mass, raising the possibility of antineoplastic activity (33).

With the above regimen, no clinical important toxicity was noted. Thus, larger doses were tested. Twenty-eight patients with no prior exposure to somatostatin were prospectively entered into a study in which 500 µg somato-

statin was self-administered three times daily by subcutaneous injections. Symptomatic improvement once again was achieved promptly in the majority of patients (flushing in 24 out of 25 patients, diarrhea in 20 of 24 and wheezing in 3 of 3 patients). Symptoms usually improved within the first few days of therapy. All 28 patients had reductions in 5-HIAA levels and in 18 out of 28 patients (64%) there was a greater than 50% reduction.

Twenty-three patients had tumor masses which could be evaluated by bidimensional measurements and/or radiographic scanning. Four out of 23 patients (17%) had >50% shrinkage of measurable tumor masses. Therapy-induced steatorrhea was common at the 500 µg three time daily dosage and one patient developed an asymptomatic gallstone. There was no evidence of hematologic, hepatic or renal toxicity.

The Mayo Clinic studies (24,32,33) along with results of other experiments (34,35) indicate that the somatostatin analogue is effective in palliating a large majority of patients with the malignant carcinoid syndrome. The associated reduction in 5-HIAA excretion appears to indicate that the clinical effectiveness of somatostatin analogue may be related to inhibition of synthesis or release of serotonin and perhaps other biogenic amines and not simply an end-organ effect. Also, there has been a report of cessation of diarrhea in a patient who was treated with the carcinoid syndrome even though the urinary levels of 5-HIAA did not decrease (31). Whether the antineoplastic effect of somatostatin is a direct effect or results from action that may be exerted indirectly by inhibiting growth hormone, insulin or perhaps other growth factors is not known.

Use of Somatostatin Analogue in Treating Patients with Carcinoid Crisis. Carcinoid crisis can be a serious, life-threatening complication of the carcinoid syndrome. It may occur spontaneously, during diagnostic evaluations, following initiation of chemotherapy, during induction of anesthesia (36) or in the intraoperative period (32).

Carcinoid crisis has been difficult to manage because of lack of response to usual measures in treating hemodynamic compromise. Fluids, crystalloid replacement, vasopressors, corticosteroids, ketanserin and tryptophan have been used with questionable benefit (37,38). Rapid reversal of life-threatening hypotension during induction of anesthesia has been accomplished by using the long-acting analogue of somatostatin (24,36,39) (Figure 8).

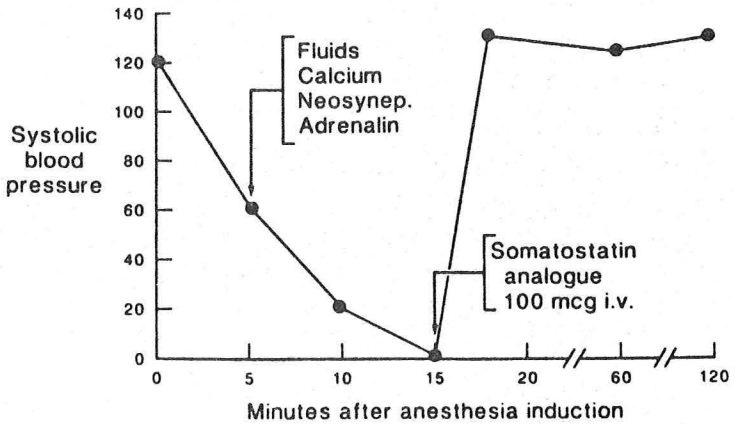

Figure 8. Effect of somatostatin analogue on decreased systolic blood pressure during carcinoid crisis during anesthesia (From Ref. 36).

The mechanism of action of somatostatin in this clinical situation is not understood completely. Somatostatin alters calcium membrane permeability and has an inhibitory effect on cyclic AMP, resulting in lower intracellular calcium and cyclic AMP levels (40). Somatostatin analogue has been shown to prevent postprandial hypotension and, in some instances, orthostatic hypotension in patients with autonomic neuropathy (41,42).

Carcinoid crisis can be induced by cancer chemotherapy. Thus, in treating patients with severe manifestations of the carcinoid syndrome, initiation of chemotherapy usually is begun with doses of drugs below what is used normally since tumor lysis may cause sudden release of vasoactive substances in massive amounts (32,43). Carcinoid crisis occurring with the administration of chemotherapy may be refractory to all standard therapy and result in death. Some physicians suggest reducing the initial dosage of chemotherapeutic agents by 50% for patients who demonstrate severe carcinoid syndrome or who have 24-hour urinary 5-HIAA levels exceeding 150 µg/24 hours. This recommendation has been made under the assumption that these patients have an increased risk of chemotherapy-induced carcinoid crisis (44). Somatostatin analogue also might be used in treating patients with severe metabolic abnormalities secondary to carcinoid syndrome to improve their clinical status prior to management with chemotherapy (45).

Somatostatin analogue is available for emergency use in patients with malignant carcinoid syndrome who are undergoing surgery, beginning chemotherapy and for treating spontaneously occurring carcinoid crisis (24). A dose of 250-500 mcg can be given subcutaneously 1 to 2 hours prior to induction of anesthesia and in acute situations, 100-500 mcg can be safely administered intravenously.

SUMMARY

Carcinoids are small tumors composed primarily of endocrine cells. These cells contain numerous peptides and amines. Some of these peptides and amines have been localized and identified but many of their functions still are unknown. Also, it is likely that many more peptides and amines will be discovered in the future.

Carcinoids originate from the endoderm or primitive gut and they all have malignant potential (some more than others). Even though they contain endocrine cells, many are "endocrinologically silent" and do not cause symptoms. Many are found at autopsy, at incidental appendectomy or during proctoscopy. Some carcinoids are more aggressive and metastasize locally and to the liver. Metastasis to the liver usually leads to carcinoid syndrome. It is this syndrome that causes a variety of signs and symptoms related to the peptides and amines produced by the endocrine cells originating from carcinoids.

When found at the time of elective surgery or by some other means such as proctoscopy, carcinoids, in general, should be resected since all tumors have some malignant potential. In most instances aggressive surgery is not warranted for well localized tumors. Aggressive surgery may be indicated in patients with tumors that have invaded tissues, such as the mesentery or tumors that have metastasized to lymph nodes.

Once the carcinoid syndrome occurs, chemotherapy is not very effective. Some treatments such as hepatic artery embolization have been useful as temporizing therapy in some patients. A somatostatin analogue has shown moderate success in treating some of the symptoms associated with the syndrome.

While the prognosis in most patients with carcinoid syndrome is better than that with other cancers, patients die as a result of metastatic carcinoids. Additionally, patients are troubled by many of the signs and symptoms of the disease. With this in mind, hopefully, future research will lead to a better understanding of the products of the tumors and their functions and also to the development of better treatments for the tumors and the syndrome they cause.

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