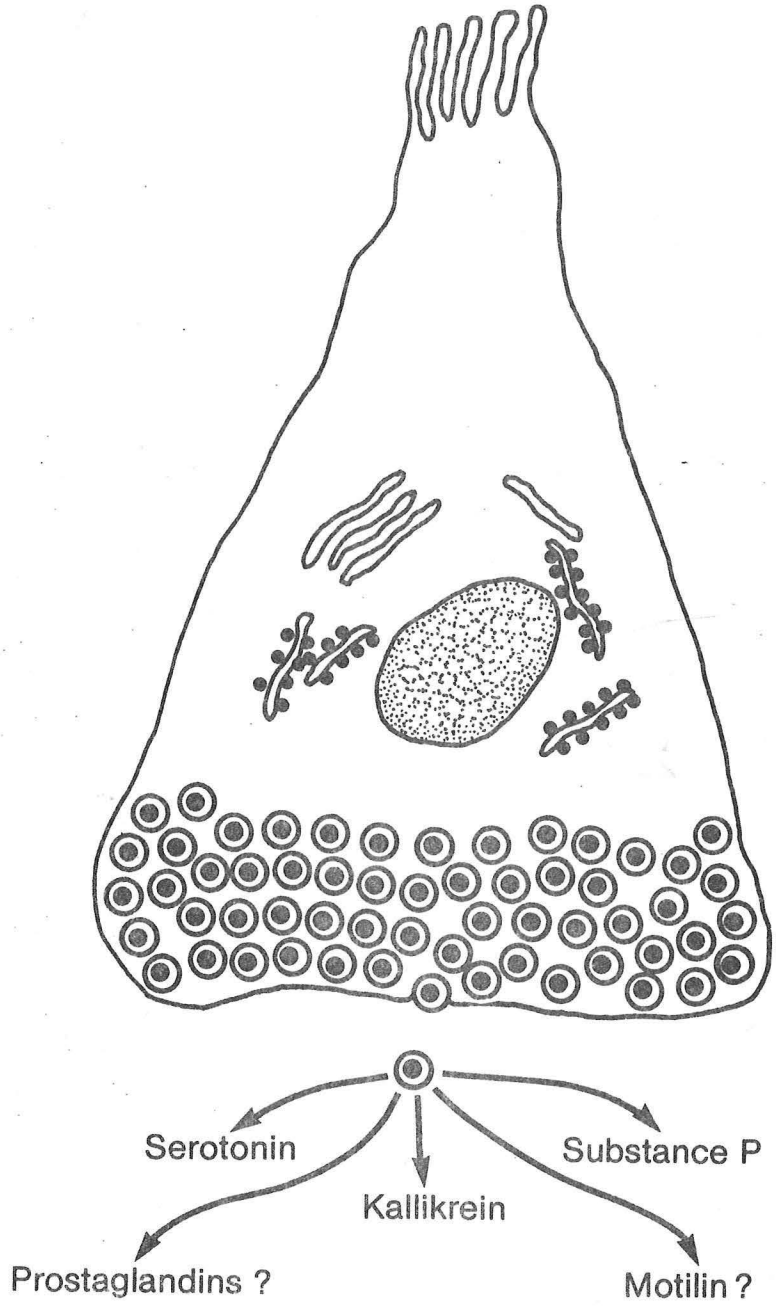
THE CARCINOID SPECTRUM

Medical Grand Rounds



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The first description of the carcinoid syndrome appeared in 1954 (Thorson et al). The spectacular symptoms associated with the syndrome attracted much attention initially and a decade later it was renamed 'The carcinoid spectrum' as variant forms of the syndrome were recognized (Sjoerdsma & Melmon, 1964). During the last decade the syndrome or spectrum has been overshadowed by the explosive development in the field of gut hormones and related tumors, so called APUDomas. Recent developments in the morphologic evaluation and classification of gut endocrine cells have now verified that carcinoid tumors are APUDomas. The purpose of this Grand Rounds is to review some of the features of the endocrine cells in the gastrointestinal tract from which carcinoid tumors are derived, outline a classification of these tumors and discuss the established and putative chemical mediators of the syndrome.

Historical developments

The first described case of a carcinoid tumor, that fulfills the later established criteria on light microscopy, without specific staining was reported in 1867 by Langhans (Uber einen Drusenpolyp im Ileum). In 1888 Lubarsch described two patients with multiple small tumors in the ileum and called these tumors "little carcinomata" to indicate a possible malignant nature of the tumors. The term 'carcinoid' tumor was introduced in 1907 by Oberndorfer in a talk before the 'German Pathology Society' in Dresden where he stressed the benign nature of the tumors (carcinoid ≅ resembling carcinoma) and suggested that the tumor might be an embryologic malformation. Simultaneous with the discovery of these tumors in the small intestine several advances were made on the light microscopy level due to the introduction of new staining techniques with identification of specific cell types in the gastrointestinal mucosa. In 1870 Heidenhahn noted that certain cells in the gut stained yellow-brown with a dichromate stain. Nicolai Kultschitzky, a Russian pathologist described in 1897 granulated cells in the crypts of Lieberkuhn in the dog and noted that the granular content in these cells changed with feeding and starvation. Due to their staining characteristics Ciaccio (1907) labelled these cells 'enterochromaffin' (EC cells). This name is still in common use although Kultschitzky's name remained an often used eponym. In 1914 Masson demonstrated that the granules of the EC cells had affinity for silver but it was not until 1928 that he could firmly establish that carcinoid tumors consisted of argentaffine cells and postulated that these tumors were derived from the EC-cell population in the gut. Masson also introduced the name argentaffinomas for these tumors. At this time the contention was still mostly in favor of the notion that these tumors were essentially benign.

Over the next few decades several case reports appeared on carcinoid tumors to a point where one author in his dismay writes: 'probably few lesions of equal obscurity have received the same degree of attention' (Dockerty, 1943) and he then spends 25 pages on this same topic! However, Dockerty was probably the first to stress that carcinoid tumors were not benign lesions and documented metastatic lesions in 13 cases out of a series of 30 patients with carcinoid tumors from the Mayo Clinic. In some of these older case reports additional symptoms or signs were mentioned such as peculiar cutaneous phenomena, diarrhea or valvular heart disease, but these findings were thought to be unrelated to the carcinoid tumor (Thorson et al,

1954). Feyrter, an Austrian pathologist, alluded to the possible endocrine nature of the EC cells in a series of paper in the German literature in the 30's and 40's (1934, 1938 & 1943) and in fact had performed some physiologic experiments with a crude extract of a carcinoid tumor on the effects on the blood pressure in a decapitated cat. Feyrter also proposed that the EC cells in the gastrointestinal tract constituted a peripheral endocrine or paracrine system, socalled 'Helle Zellen' system (1953). Feyrter's papers, however, remained largely ignored, but were later recognized by Pearse (1968) when he introduced the APUD system. The chemical nature of the postulated excretory product of the EC cells remained elusive up to 1952 when Erspamer & Asero reported that serotonin was found in the EC cells and the following year Lembeck (1953) isolated that same substance from a carcinoid tumor. Serotonin had only been identified a few years before by Rapport (1948) who had isolated a vasoconstrictor factor from beef serum, hence the name, and further demonstrated that serotonin stimulated intestinal motility. In 1952 Biörck et al reported on one patient with ileal carcinoid, liver metastases and a peculiar intermittent cyanosis. The patient also had right-sided valvular heart disease which was thought to be congenital. The same year one of the authors, Jan Waldenström, saw another patient who had a documented malignant carcinoid tumor with liver metastases, paroxystic flushes exactly as the first patient and pulmonary stenosis. Jan Waldenström's clinical intuition led him to believe that this unusual combination of symptoms in two patients with a carcinoid tumor was more than a mere coincidence and constituted a syndrome. From a careful search of the medical literature the Swedish group was able to find 16 cases of metastatic carcinoid tumors and additional symptoms. This series was published in 1954 in the 'American Heart Journal' under this impressive title:

American Heart Journal

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Original Communications

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

A CLINICAL AND PATHOLOGIC SYNDROME

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which lists the now classical features of the carcinoid syndrome except diarrhea. In addition, Thorson et al postulated that a common denominator, serotonin, was responsible for the diverse symptoms. In 1953 Rosenbaum et al (U.S.A.) and Isler & Hedinger (Switzerland) had reported on 2 and 3 patients, respectively, with metastatic carcinoid and pulmonary stenosis and both papers alluded to a new syndrome, but Thorson et al's report is now considered the classic paper that delineated the new syndrome. In the intervening years an abundant number of papers have appeared on carcinoid tumors and syndrome arising not only in the gut, but also in bronchial adenomas, thymus and ovarian teratomas which points to a more widespread distribution of EC cells.

EC Cells

The enterochromaffin cells are dispersed among the epithelial cell at the base of the glands in the stomach and at the base of the crypts in the intestine and are found from stomach to rectum, but not in the esophagus. The cells appear light on conventional staining (Feyrter's 'Helle Zellen') and stain in a characteristic fashion with a chrome or silver-stain. On electronmicroscopy the cells are flask-shaped with a broad base on the basal membrane and a narrow upper part with a few microvilli on the luminal surface. The Golgi complex is well developed and located in the supranuclear portion of the cell. In the infranuclear region there is an abundance of secretory granules. The particular staining characteristics of the EC cells are due to the secretory granules which may vary widely in diameter and shape. The argentaffine cells are characterized by their ability to reduce Ag^{+} ions to metallic silver and the silver stains are concentrated on the secretory granules. The reducing substance is serotonin or a closely related derivative (Barter & Pearse, 1953). Many of the gut endocrine cells are, however, nonargentaffine, but argyrophil which means that they only stain with a silver preparation when a reducing substance is added (Grimelius, 1980). The chemical basis for the argyrophil reaction is unknown, but appears to be unrelated to amine content (Solcia, 1976). The serotonin containing granules can also be demonstrated by formaldehyde-induced fluorescence (Falck et al 1962; Enerbäck, 1973) where formaldehyde converts serotonin to a fluorophore (dihydrocarboline) with a yellow fluoroscence and a characteristic emmision spectrum. Argentaffine carcinoids are fluorescence positive whereas argyrophil carcinoids are negative. As carcinoid tumors can be either argentaffine or nonargentaffine the term argentaffinoma is no longer tenable for these tumors. On the electronmicroscopy level it has been observed that the morphology of the secretory granules varies significantly in different cell population of the endocrine cells in the gut, but is fairly uniform within the same cell population (Solcia, 1979). However, it is not possible to identify the specific cell types based on granule morphology alone.

With the introduction of more sensitive assays such as radioimmunoassay the gut hormone concept has flourished over the past two decades and the number of verified or potential candidate hormones has increased exponentially. Immunocytochemical investigations with fluorescent-labeled antibodies raised against presently known gut and pancreatic hormones have elucidated the distribution and localization of the hormones within specific cells and neurons in the gastrointestinal tract. The endocrine cells are widely dispersed in the gastrointestinal epithelium and Polak & Bloom (1979)

have proposed the term 'The Diffuse Endocrine System' to encompass all endocrine cells within the gut and in contradistinction to a classical endocrine gland where a specific cell type is confined to a glandular structure. Besides sharing common morphologic features on light and electronmicroscopy, the endocrine cells also share certain cytochemical characteristics namely the ability of Amine Precursor Uptake and Decarboxylation (APUD) as shown by Pearse (1968). The APUD concept was introduced to characterize a series of endocrine cells such as the thyroid C-cell, chromaffine cells in the adrenal medulla, pancreatic islet cells and the endocrine cells in the gut and to propose a common origin of these cells from ectoderm of the neural crest. Pearse has over the years strongly propounded the neural crest orgin of the APUD cells (1969, 1974,1975). This concept has, however, been attacked by several investigators who in embryologic studies with removal or transplantation of the neural crest could not confirm a neural crest origin and suggested an endodermal development (Le Douarin et al, 1970, 1973; Andrew et al, 1974; Leblond & Cheng, 1976; Pictet et al, 1976). In 1976 Pearse redefined his concept to state that 'all peptide hormone producing cells are derivatives of specialized ectoderm and therefore, effectively of cell lines derived from the epiblast and programmed for ultimate neuroendocrine function.' The discovery that several gut hormones are also synthesized in the brain (Pearse, 1976) lends some support for an ectodermal derivation but the issue is still not resolved.

With the aid of staining characteristics and especially from immunocytochemistry the gut endocrine cells have been classified into a steadily increasing list of cell types designated by letters. The list has been revised several times and the current list (Solcia, 1981) includes 18 different cell types as shown in Table I.

Table I. Human Gastroenteropancreatic endocrine cells

Cell	Main Product	PANCREAS	STOMACH		INTESTINE		
					Small		
			Oxyntic	Antral	Upper	Lower	Large
P	Peptides?	a	+	+	+		
D_1	Peptides?	f	+	f	f	f	f
EC	5-HT, Peptides	r,b	+	+	+	+	+
D	Somatostatin	+	+	+	+	f	f
B	Insulin	+					
PP (F)	Pancreatic polypeptide	+					
A	Glucagon	+	a,b				
X	Unknown		+				
ECL	Unknown (b:histamine)		+				
G	Gastrin			+	f		
IG	Gastrin			b	+	r	
TG	C-terminal gastrin/CCK			b	+	b	
I	CCK				+	f	
S	Secretin				+	f	
K	GIP				+	f	
Mo	Motilin				+	f	
N	Neurotensin				r	+	r
L	GLI				f	+	+

a = foetus or newborn; b = animals; f = few; r = rare; GLI = Glucagon-like immunoreactivity

As is apparent several cell types are only defined morphologically and a possible peptide hormone content has not been identified. The silver staining characteristics of all these cells types have recently been reexamined (Grimelius & Wilander, 1980) with one argentaffine stain and three different silver techniques to demonstrate argyrophilia as shown in Table II.

The argentaffin and argyrophil reaction in different types of endocrine cells of the human gastrointestinal tract and pancreas

Type of cell*	Hormone	Masson	Grimelius	Sevier-Munger	Davenport
P	Bombesin-like	–	+	+†	–
EC_1	Serotonin + substance P	+++	+++	+++	–
EC_2	Serotonin + motilin	+++	+++	+++	–
D_1	Nk	–	+	+†	±
PP	Pancreatic polypeptide	–	+‡	+‡	–
D	Somatostatin	–	–	–	+++
B	Insulin	–	–	–	–
A	Glucagon	–	+++	±§	–
X	Nk	–	+	(+)	–
ECL	Nk	–	+++	+++	–
G	Gastrin	–	+	±§	–
S	Secretin	–	+	±§	–
I	Cholecystokinin	–	–	±	–
K	Gastric inhibitory peptide	–	+++	+++	–
N	Neurotensin	–	+	–	–
L	Glicentin	–	++‡	±	–

±±± strong silver reaction; ++ fairly strong silver reaction; + weak silver reaction; ± sometimes weak silver reaction, sometimes unreactive; (+) practically unreactive; – non-reactive; Nk not known.
* See the Lausanne 1977 classification (SOLCIA *et al.*, 1978).

Only two cell types, EC_1 and EC_2, are argentaffine and these cells are commonly found in the small intestine (midgut). The distinction into two different argentaffine cell populations is based on hormone content. Substance P (SP) and motilin have been identified in EC_1 and EC_2, respectively (Nilsson et al, 1975; Polak et al, 1975; Capella et al, 1977; Heitz et al, 1976 & 1978) with immunocytochemical stains. The classic carcinoid tumor is derived from EC_1 or EC_2 cells. The majority of cells types, however, are nonargentaffine, but argyrophil to a varying extent. The Grimelius silver stain reacts with most of the cells except pancreatic B and D cells and cholecystokinin containing I cells. The nonargentaffine carcinoid tumors are derived from the ECL cells in the stomach (foregut) and the L cells in the large intestine (hindgut). The ECL cells have a high histamine content in lower animals, but not in man and a possible peptide hormone product remains to be identified. The L cells react with antiglicentin sera (glicentin = proglucagon) but carcinoid tumors arising in the hindgut are usually silent from an endocrine point of view. The endocrine tumors of the gut are still poorly defined. Solcia (1981) has recently proposed a classification based on function as outlined in Table III

Table III Endocrine tumours of the gut

A. Functionally defined tumours:
   —Gastrin cell tumour (gastrinoma)
   —D-cell tumour (somatostatinoma)
   —L-cell tumour (enteroglucagonoma)
   —EC cell tumour (argentaffin carcinoid)
      1. 5-HT with Substance P
      2. 5-HT without Substance P
   —Ectopic tumours (ACTH, HCG, insulin, etc.)

B. Functionally undefined tumours
   (Non-argentaffin carcinoids):
      1. ECL cell carcinoid
      2. P-D_1 cell carcinoid
      3. Paraganglioma
      4. Others

C. Poorly differentiated endocrine carcinoma
   (Argyrophil carcinoma; endocrine microcitoma)

where the tumors are divided into three groups. The first group (A) consists of functionally defined tumors arising from a distinct cell population identified by immunocytochemistry and producing a distinct clinical syndrome due to the hormone production such as gastrinomas and somatostatinomas. The classic carcinoid tumors belong to this group. The second group (B) are functionally undefined tumors where the cell population is identified by electronmicroscopy, but the tumor product, if any, is still not identified. The nonargentaffine carcinoids are included in this group such as ECL and P-D, cell carcinoids found in the stomach where ECL cell carcinoids predominates. The last group (C) includes tumors composed of poorly differentiated argyrophil cells. The VIPomas should probably be included in this group as they are thought to develop from neoplastic transformation of endocrine cells. Despite intensive search VIP containing cells have not been found in the gut or pancreas in man.

The Carcinoid Tumors

The development from a normal endocrine cell population to hyperplasia and to tumor has been observed in a few cases of gastric carcinoids (Black et al, 1967; Larson et al, 1978; Harris et al, 1978; Wilander et al, 1979;

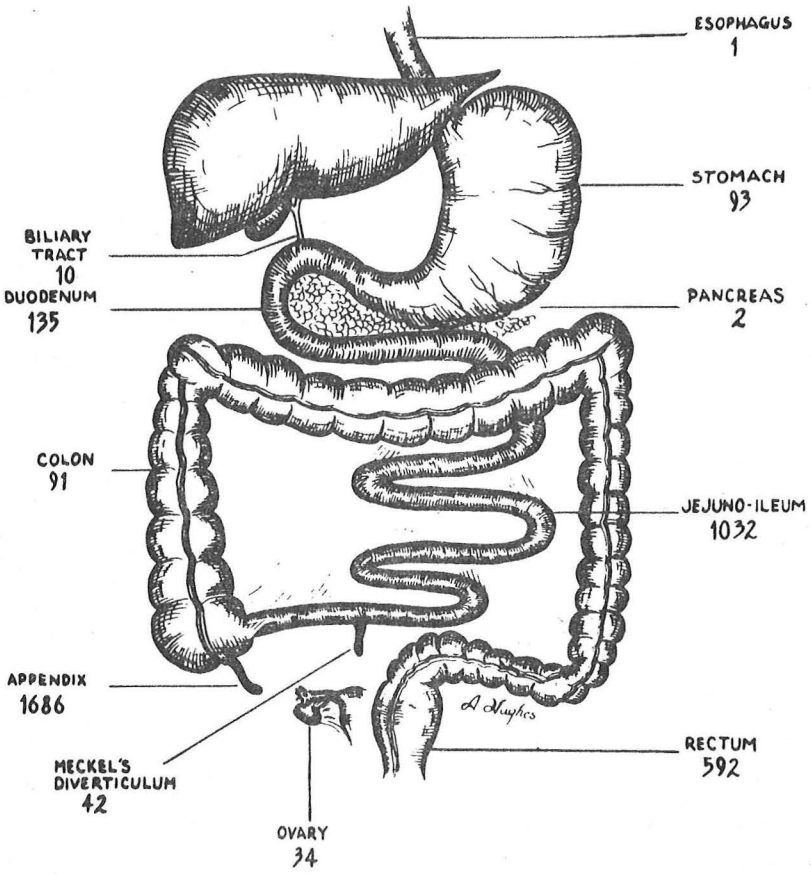
Abrams, 1980; Hodges et al, 1981). All cases described so far had achlorhydria and markedly elevated S-gastrin, diffuse hyperplasia of the argyrophil cells and carcinoid tumors, which were multiple in several cases. In a few cases the proliferating cells were identified as ECL cells. Further, in patients with Zollinger-Ellison syndrome and gastric mucosal hypertrophy, argyrophil cell hyperplasia is seen regulary and a condition called microcarcinoidosis has been described with intramucosal argyrophil nodules (Bordi et al, 1974). This finding supports the notion that gastrin acts as a trophic hormone on the endocrine cells in the stomach. This has been substantiated in animal experiments where S-gastrin levels can be reduced or increased by antrectomy or antral exclusion. In antrectomized rats, the argyrophil cell population decreased significantly whereas antral exclusion was followed by a marked increase (Håkanson et al, 1976). Whether the growth rate of the other endocrine cells from which carcinoid tumors are derived in other areas of the gastrointestinal tract is under trophic regulation by hormone(s) is still unknown.

Incidence and Distribution

The true incidence and prevalence of carcinoid tumors are unknown. In several large autopsy series the average frequency of carcinoid tumors was about 0.5% (Donald, 1956; Moertel et al, 1961,). Feyrter (1962) who had a special interest in carcinoid tumors found a frequency of 1.4% in a series of 2.500 autopsies. In a recent report from Malmö, Sweden where they continue to pay particular attention to carcinoid tumors a frequency of 1.2% was found (Berge & Linell, 1976). This series covered 16.300 autopsies over a 12 year period from a restricted area where approximately 60% of all who die have an autopsy. More than 90% of all carcinoids were an incidental finding and could not be attributed to the immedicate cause of death. The fact that so many carcinoid tumors were incidental findings implies a slow growth rate. The Malmo group further found that multiple carcinoids were present in about 30% and similarly metastases to lymph nodes and liver were present in about 30%. Only one case of the carcinoid syndrome was observed among the 199 cases of carcinoid tumors in this 12 year period.

Carcinoid tumors may arise anywhere in the gastrointestinal tract except esophagus and usually appears as a yellow submucosal nodule. The size of the primary lesion may vary from less than 1 cm up to 2-3 cm and often the primary lesion remains undetected despite extensive metastases. In a review of carcinoid tumors Cheek & Wilson (1970) collected 3718 cases from the world literature. The distribution of the tumors is shown in Figure 1.

FIG. 1.—Total collected series of carcinoid tumors.



Carcinoid tumors in the ovary have been included, but tumors arising in bronchial adenomas were excluded. Appendiceal carcinoid (45%) is the most common location followed by small intestine (28%) in particular in the ileum, and rectum (16%). These three locations account for about 90% of all the cases. The propensity to metastasize varied widely as shown in Table IV

—TOTAL COLLECTED SERIES OF CARCINOID TUMORS

SITE	CASES	AVERAGE % METASTASIS	CASES OF CARCINOID SYNDROME
Esophagus	1	—	0
Stomach	93	23	8
Duodenum	135	20	4
Jejuno-ileum	1,032	34	91
Meckel's diverticulum	42	19	3
Appendix	1,686	2	6
Colon	91	60	5
Rectum	592	18	1
Ovary	34	6	17
Biliary tract	10	30	0
Pancreas	2	—	1
	3,718		136

from 2% up to 60% with the appendiceal carcinoid being least likely to metastasize. The low incidence of metastases from appendiceal carcinoids is probably due to the fact that tumors in this location may produce symptoms suggestive of acute appendicitis and thus early removal, or that many appendices are removed per occasionem, some of which may contain a carcinoid tumor. The tumors in cecum and colon has the highest percentage of metastases probably because the primary lesions remain asymptomatic until they reach a considerable size. The size of the primary lesion is correlated to the incidence of metastases. In a series of 209 cases from the Mayo Clinic, Moertel et al (1961) found metastases in 2% of cases when the tumor was less than 1 cm, whereas 50% of lesions greater than 1 cm and 80% of lesions greater than 2 cm metastasized.

Bronchial carcinoid tumors arise in bronchial ademonas which account for about 6-10% of primary lung tumors. The tumors are usually found in the main bronchi and are polypoid. The bronchial carcinoids are derived from nonargentaffine endocrine cells in the bronchial epithelium. A specific hormone content within these cells has not been identified. The carcinoid tumors in the ovary are usually found within a teratoma.

There appears to be no specific pathology other than metastases that differentiates the tumors which produce the carcinoid syndrome from those that do not. The manifestation of the carcinoid syndrome in association with gastrointestinal carcinoids seems to depend in most cases upon the presence of

hepatic metastases. In some cases, however, the syndrome may occur in the presence of large lymphnode metastases with few or no hepatic metastases. The usual association of the syndrome with hepatic metastases is explained in two ways. Before metastases occur the tumor products are effectively metabolized to inactive products in the liver. When hepatic metastases are present the tumor products will drain into the systemic circulation through the hepatic veins thus escaping hepatic inactivation. Secondly, the hepatic metastases form a considerable tumor mass much larger than the primary site, and the amount of tumor products released may thus be increased proportionally. In Cheek & Wilson series (1970) (Table 4) 136 cases of the carcinoid syndrome (3.7%) were found of which 75% arose from small intestinal carcinoids. A frequency of 3.7% of all carcinoid tumor producing the carcinoid syndrome is an overestimate as the number of carcinoid tumors in their collected series does not reflect the true prevalence as many cases remain asymptomatic throughout life. In Berge & Linell's(1976) autopsy series the frequency was only 0.5% which is probably closer to the truth. The low frequency again stresses the rarity of the carcinoid syndrome. By extrapolation from the Malmö frequency a case of the carcinoid syndrome should be detected every 2 or 3 year in the Dallas area.

Morphology of Carcinoid Tumors

When the carcinoid tumors were described originally they were identified by staining characteristics (enterochromaffine or argentaffin) and characteristic localization (appendix, small intestine) and structure (Masson, 1928). It became apparent, however, that the tumors may be nonargentaffin and may arise in other areas in or outside the gastrointestinal tract and may display unusual biochemical features. Williams & Sandler (1963), therefore, proposed a new classification of carcinoid tumors based on embryologic orgin (foregut, midgut and hindgut) with the following characteristics (Table 5).

CHARACTERISTICS OF CARCINOID TUMORS OF THE GUT

	FOREGUT	MIDGUT	HINDGUT
HISTOLOGICAL STRUCTURE	Trabecular	Nestlike	Trabecular
ARGENTAFFINITY	Negative	Positive	Negative
ASSOCIATED WITH CARCINOID SYNDROME	Yes	Yes	No
TUMOR SEROTONIN CONTENT	Low	High	Not Detected
URINARY 5-HIAA EXCRETION	High	High	Normal
5 HTP SECRETION	Frequent	Rare	Not Detected
METASTASES TO BONE AND SKIN	Common	Rare	Common

Sandler, 1963

The foregut carcinoids (bronchial, stomach and duodenum) have a distinct trabecular pattern, are nonargentaffin and usually have a low serotonin content, whereas midgut carcinoids have a nestlike structure, are argentaffin with a high serotonin content. The hindgut carcinoids usually have a mixed histological structure, are nonargentaffin with no detectable serotonin content. The tumors also differ with respect to association with the carcinoid syndrome and site of metastases. The distinct histologic features and staining characteristics of fore-, mid- and hindgut carcinoid tumors were confirmed by Soga & Tazawa (1971) in a histologic reevaluation of 62 carcinoid tumors. They stressed that some carcinoids may have histologic structures of lower or atypical differentiation which are difficult to distinguish from adenocarcinoma with conventional light microscopy, but can be classified as a carcinoid if secretory granules are found by electronmicroscopy. They further suggested the following criteria to document a carcinoid tumor (Table VI).

MORPHOLOGIC CRITERIA IN THE DIAGNOSIS OF CARCINOID TUMORS

1. Routine Morphology (Hematoxylin-Eosin)
   a. Classic Pattern (Nestlike or Trabecular)
   b. Mixed Pattern or Less Differentiated

2. Silver Staining
   a. Argyrophil (Grimelius Stain)
   b. Argentaffine (Masson-Fontana Stain)

3. Electronmicroscopy
   a. Specific Secretory Granules

4. Histochemistry
   a. Serotonin
   b. 5-Hydroxytryptophan
   c. Histamine

5. Immunocytochemistry
   a. Substance P
   b. Motilin
   c. Neuron Specific Enolase

The list has been modified to include recent developments in immunocytochemistry. Often the diagnosis of a carcinoid tumor can be made when the first two criteria are fulfilled and only in special cases is electronmicroscopy indicated. Immunocytochemical identification of the specific hormone content is only available in a few research laboratories. Pearse's group in London has recently introduced a new immunocytochemical staining technique, neuron-specific enolase, that appears very promising to distinguish between endocrine and non-endocrine tumors (Tapai et al, 1981). Neuron-specific enolase is a neuronal isomer of the widely distribituted glycolytic enzyme enolase and was first isolated from brain tissue and later shown to be present in neurons and APUD cells (Marangos 1978 & 1979). An antibody was raised against this enzyme and used for immunostaining in 90 previously well documented APUDomas (9 carcinoid tumors) and in 11 nonendocrine gastrointestinal carcinomas. All 90 APUDomas were neuron-specific enolase positive whereas all 11 carcinomas were negative. When this antibody becomes commercially available the distinction between endocrine and nonendocrine tumors should be greatly facilitated.

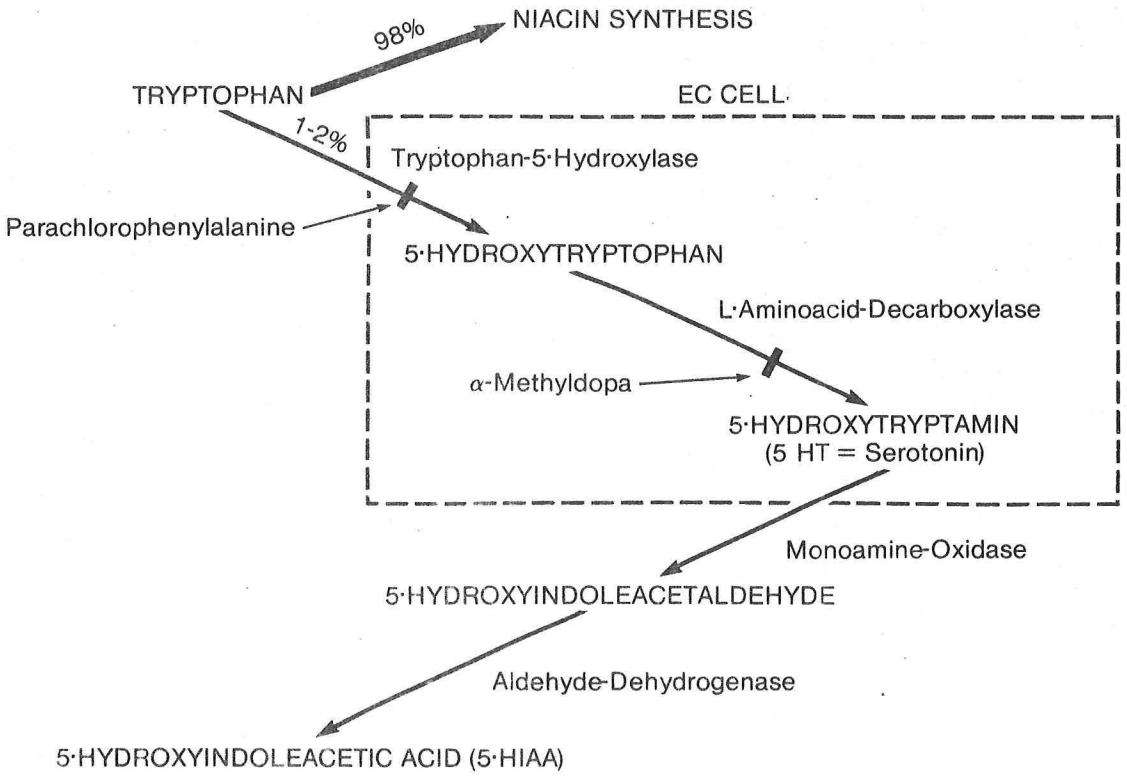
BIOCHEMICAL MEDIATORS OF THE CARCINOID SYNDROME

Serotonin:

When the carcinoid syndrome was first described (Thorson et al, 1954), serotonin had just been identified in the argentaffin cells and in carcinoid tumors (Erspamer, 1952, Lembeck, 1953). Thus, not surprisingly it was initially thought that serotonin was the common denominator of the diverse symptoms in the syndrome.

The EC cells belong to APUD system and accordingly have the capacity for uptake of aminoacids and amine production. Tryptophan is the precursor for serotonin and normally about 1-2% of the tryptophan pool is converted to serotonin, as shown in Figure 2,

TRYPTOPHAN METABOLISM IN EC CELLS



by hydroxylation (trytophan 5-hydroxylase) and decarboxylation (aromatic L-amino acid decarboxylase) in the cytoplasm of the EC cells. Serotonin is transported to and stored in the secretion granules together with a peptide hormone (Substance P, Motilin) (Alumets et al, 1977; Sundler et al, 1980). The secretory granules are released from the EC cells by exocytosis where the granules fuse with basal membrane and release their contents to the immediate environment. Ahlman (1976) has shown that vagal excitation lowers the serotonin content in the EC cells, but presumably luminal stimuli may have the same effect by a still unknown mechanism (Solcia et al. 1979). It is similarly unknown why serotonin is stored with a peptide hormone and whether serotonin has any physiologic function locally (paracrine) or systemically. Once released serotonin is rapidly deaminated and oxidised via MAO (liver, lung, kidney) to 5-hydroxyindoleacetaldehyde and further oxidised to 5-hydroxyindoleacetic acid (5-HIAA) which is the main excretory product. In some foregut carcinoids, there is a relatively lack of decarboxylase and the tumors then contain and release 5-hydroxytryptophan (5-HTP) (Sandlers & Snow, 1958; Oates & Sjoerdsma, 1962; Campell et al, 1963; Feldman, 1978) 5-HTP is converted in the periphery to serotonin and 5-HIAA and patients with these tumors have increased urinary excretion of 5-HTP, serotonin and 5-HIAA. In a few cases of gastric carcinoids an increased excretion of histamine has been observed (Waldenstrom & Ljungberg 1956, Oates & Sjoerdsma 1962, Feldman 1978). These tumors obviously have an increased uptake of histidine which is converted to histamine via histidine decarboxylase.

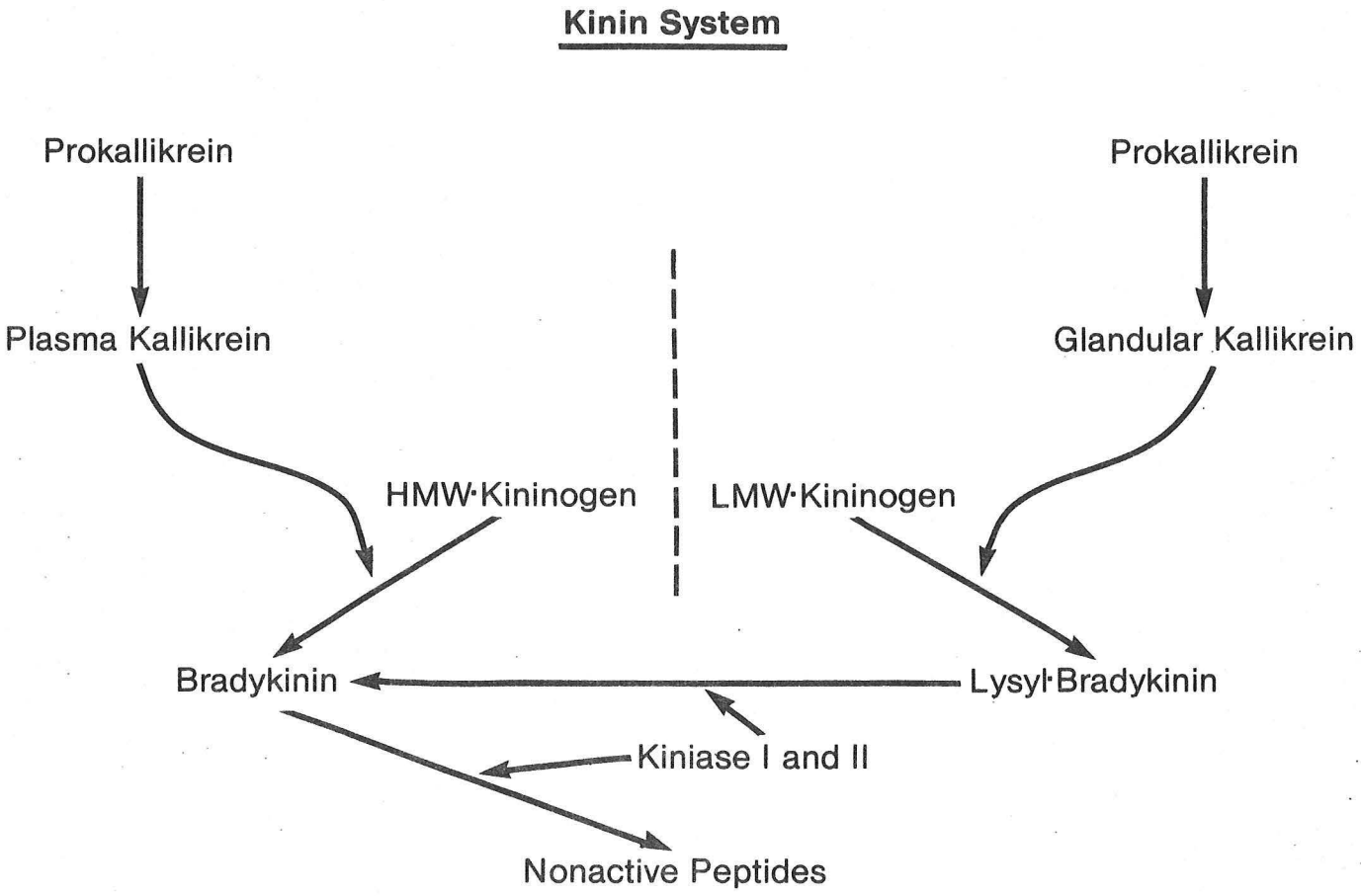
The upper normal limit of urinary 5-HIAA excretion is 10 mg/24 h and almost all patients with the carcinoid syndrome have a markedly elevated 5-HIAA excretion and this test remains the most reliable in identifying patients with the syndrome (Feldman 1978). In most laboratories urinary 5-HIAA is still determined by a color reaction with nitrosonaphthol to give a purple color (Udenfriend et al, 1955) but many other products may intefere with this reaction to give false positive results and ingestion of certain foods (bananas, pineapple, walnut) or drugs (acetanilid, mephenesin) may produce a falsely elevated urinary 5-HIAA. Recently, a more sensitive liquid chromatographic assay that is free from interferences of other color products in the urine has been introduced (Shihabi & Scaro, 1980).

Serotonin synthesis is blocked by parachlorophenylalanine at the 5-hydroxylase step and by α-methyldopa at the decarboxylase step and the peripheral actions of serotonin is antagonized by methysergide and cyproheptadine. While the overproduction of serotonin in the carcinoid syndrome is well documented, it soon became evident that serotonin could not be the sole mediator of all symptoms in the carcinoid syndrome as treatment with these drugs were only effective against one of the symptoms, namely diarrhea (Sjoerdsma et al, 1970). Further, it was shown that an increase in serum serotonin was not correlated to flushing episodes and that infusion of serotonin at best produced an atypical flush (Robertson et al, 1962), which stimulated a search for other chemical mediators.

Kinins

In 1964 Oates et al reported that plasma bradykinin was increased during flushing episodes in patients with the carcinoid syndrome and that kallekrein

activity was significantly elevated in liver metastases in 6 patients with the syndrome. The kallikrein-kinin system has received increasing attention recently and the kinins have been implicated in many biologic actions (Erdös, 1976). There are two kallekrein-kinin systems, one in plasma and one in exocrine glands (pancreas, kidney), and plasma and glandular kallikrein are distinct chemically and enzymatically and are functionally different (Figure 3).



Plasma kallikrein is activated from a proenzyme by the Hageman factor and acts on high molecular weight (HMW) kininogen in α_2-macroglobulin to release bradykinin whereas glandular kallikrein preferentially acts on low molecular weight (LMW) kininogen to release lysylbradykinin. The enzymes kininase I and II convert lysylbradykinin to bradykinin and further convert bradykinin to inactive peptides. Kininase II is identical to angiotensin-converting enzyme. The kinins have a very short half-life in plasma (seconds) but have pronounced systemic effects such as vasodilation, hypotension, flushing and brochoconstriction which resemble some of the manifestations of the carcinoid syndrome. The physiologic function of the kallikrein-kinin system is unknown, but it has been speculated that the system may be involved in the local regulation of blood flow and maybe also in the systemic regulation of blood pressure as the angiotensin converting enzyme is a key enzyme in both the kallekrein-kinin system and the renin-angiotensin system with opposing effects on the vasculature.

When bradykinin is infused into patients with the carcinoid syndrome a flushing reaction results that mimics the spontaneous flushes (Adamson et al, 1969). Furthermore, elevated bradykinin level correlate with the flushing episodes in most patients, but not in all (Oates et al 1964; Adamson et al, 1969). Bradykinin stimulates smooth muscle activity in the gut and decreases water and electrolyte absorption (Crocker et al, 1975; Hardcastle et al, 1977). A kallikrein inhibitor that functions in-vivo is still not available. Aprotinin (Trasylol) requires preincubation with kallikrein to produce inhibition and has not been tested in patients with the carcinoid syndrome.

Prostaglandins:

The kinins interact with the prostaglandin system and increase the synthesis of PGE and PGI_2 (prostacyclin) (McGiff et al 1980a, 1980b; Nasjletti et al, 1981). Since PGE and prostacyclin can both produce flushing and diarrhea when administered in man (Smith & Mason, 1974) it is not surprising that these ubiquitous molecules have been implicated as mediators of the carcinoid syndrome. Over the last decade several case reports have demonstrated elevated prostaglandin levels (blood or urine) in patients with this syndrome (Sandler et al, 1968; Feldman et al, 1974; Smith & Greaves, 1974; Delmant & Rampal, 1975). Metz and associates (1981) have recently critically reviewed all reported cases of carcinoid syndrome and associated elevated prostaglandin levels and included a study of 8 of their own patients. They used the following three criteria to document an effect of prostaglandins in the production of symptoms (Table VII).

CRITERIA FOR DOCUMENTING A ROLE OF A PUTATIVE MEDIATOR IN THE CARCINOID SYNDROME

1. The mediator can reproduce the sign or symptom.
2. The mediator is produced in absolute or relative excess either by or in response to a product from the carcinoid tumor.
3. Inhibition of the synthesis of the mediator reverses or ameliorates the sign or symptom.

Modified from Metz, 1981

None of the reported cases fulfilled all three criteria and several of the reviewed reports lacked adequate control data or had unacceptable high control values. Furthermore, in Metz et al's series of 8 patients, where prostaglandin concentrations were measured with a sensitive radioimmunoassay, the prostaglandin levels were normal and did not increase during provacation tests. None of the patients observed amelioration of the symptoms when prostaglandin synthesis was inhibited with indomethacin. Thus, a role for prostaglandins in the carcinoid syndrome is still not documented.

Substance P:

Substance P (SP) was first isolated from brain tissue (vonEuler & Gaddum, 1931) and for many years the structure and function of this substance remained a puzzle (P = preparation). The aminoacid sequence is now known (Chang & Leeman, 1970), and its synthesis has been accomplished (Leban et al, 1979). SP belongs to a group of peptides called tachykinins. The other compounds in this group with the rather exotic names, eledoisin and physalaemin, have been isolated from amphibian skin. After the structure was identified several investigators produced antibodies to SP and used these as an immunocytochemical tool to identify SP containing cells and found SP in the EC cells of the small intestine (Nilsson et al, 1975; Heitz et al, 1976 & 1978). The EC cells with SP content was later subclassified to EC_1 cells (Solcia, 1981; Table 3).

The primary function of SP appears to be a neurotransmitter in the afferent sensory system both in the brain and peripherally. The intestine has an abundant network of SP staining neurons besides the isolated SP-positive EC_1 cells (Schultzberg et al, 1980).

Two groups have found a high content of SP in carcinoid tumors of midgut origin (Hakanson et al, 1977; Skrabanek et al, 1976 & 1980). Recently, Skrabanek et al (1978) found an approximately fourfold elevation of plasma SP and even higher concentrations in the veins draining the tumors in 3 patients with the carcinoid syndrome. Alumets et al (1977) have isolated the cytoplasmic granules from an ileal carcinoid tumor and demonstrated that the granules contained both serotonin and SP immunoreactivity.

SP has many physiologic effects similar to bradykinin and prostaglandins. When infused in man SP causes a bright red flush, hypotension, tachycardia and increased intestinal motility (Skrabanek et al, 1978). Walling et al (1977) have shown that SP causes a decrease in sodium absorption and changes chloride absorption to secretion in rat ileum without any change in intracellular cyclic nucleotide levels (cAMP and cGMP). Thus SP acts as a secretagogue by a still unknown mechanism. The effects of SP are not mediated via prostaglandins as inhibition of prostaglandin synthesis does not antagonize the effects (Lembeck et al, 1976). Only very recently has an antagonist to SP been synthesized (Folkers et al, 1981). This antagonist completely abolishes the effect of SP on smooth muscle contractions in guinea pig ileum.

SP appears to be an attractive mediator in the carcinoid syndrome but until it can be demonstrated that an SP antagonist alleviates some of the symptoms, it remains a putative mediator.

Motilin:

Motilin was isolated in 1971 (Brown et al) and is found in relatively high concentrations in the proximal small intestine in the EC_2 cells (Polak et al, 1975). The physiologic functions of motilin is still debated. Initially, motilin was thought to regulate the interdigestive myoelectric complex (Vantrappen et al, 1979) but suppression of motilin activity does not inhibit the initiation of the motor complexes (Christofides & Bloom, 1980). Moreover, evidence for an increased concentration of motilin in plasma or tumors in the carcinoid syndrome is still lacking. Motilin still appears to be a candidate hormone without any defined physiologic function.

SYMPTOMATOLOGY OF THE CARCINOID SYNDROME

The Carcinoid Flush:

The characteristic flush is the most frequent symptom in the carcinoid syndrome seen in more than 90% of reported cases (Grahame-Smith, 1972) and usually precedes the other symptoms by several years. The flush is most pronounced in the face, neck and upper extremities, but may involve the whole body. In the older literature the flush is described very elaborately. In the presumed first reported case of the carcinoid syndrome, although not recognized as such at the time, Sir Maurice Cassidy described the patient as follows: 'a phenomenal flushing of face, much exaggerated during emotion or during a meal and numerous dilated venules of recent origin over the nose and cheeks. The skin of the trunk was usually of a mottled mauve color with sudden changes to a vermillion hue' (1930). The description also illustrates that these patients develop chronic skin changes with telangiectasia with

time. The flush may be provoked by food intake, alcohol, palpation of the enlarged liver or develop spontaneously. Grahame-Smith (1972) has divided the flush reaction into 4 distinct types. Types 1 and 2 are only qualitatively different in that type 2 is of a more violaceous to cyanotic color, but affects the same area as type 1. Type 3 is usually associated with bronchial carcinoid tumors, is of a lighter red color, may involve the whole body and last for hours to days. Type 4 is seen with histamine-producing gastric carcinoids, is patchy, bright red and often most pronounced around the neck. The distinction in these 4 types is mainly of academic interest as most physicians will see only a few cases of the carcinoid syndrome in their lifetime.

Bradykinin is the best established mediator of the flush, but the evidence is still circumstantial until a kallekrein inhibitor or a bradykinin antagonist is developed. Levine & Sjoerdsma (1963) introduced a provocation test for the flushing attack with epinephrine or norepinephrine (3-6 μg i.v.) which produce severe flushing and hypotension in patients with the carcinoid syndrome. Phentolamine, an α-adrenergic blocker, will prevent an epinephrine induced flush, but not a bradykinin induced flush (Adamson, 1969). Whether the catecholamines act on the carcinoid tumor to release kallikrein is an attractive, but unproved hypothesis. The type 4 flush is probably only produced by histamine as this flush is effectively blocked by a combination of H_1 and H_2 blockers (Roberts et al, 1979). Recently, Fröhlich et al (1978) reported that pentagastrin infusion induced severe flushes in 3 patients with the carcinoid syndrome and that somatostatin completely prevented the flushes. The mechanism by which pentagastrin induces a flush is unknown; somatostatin, however, has been shown to inhibit gastrin release and action (Barros et al, 1975). Further, somatostatin has been found to be of therapeutic value during surgery in patients with carcinoid tumors who may develop severe flushing, hypotension or bronchoconstriction (Thulin et al, 1978). The symptomatic treatment of type 1, 2 & 3 flushes is still inadequate. α-adrenergic blockade is only effective in a limited number of patients and the side effects (hypotension, drowsiness) often prevent their usage (Levine & Sjoerdsma, 1963).

Diarrhea:

Diarrhea is almost as common as flushing in the carcinoid syndrome (85%). The diarrhea is often watery and the patients may have multiple bowel movements per day. It persists during fasting and in the few patients where stool osmolality has been measured, the osmolality corresponds to plasma, indicating a secretory type of diarrhea. Intestinal perfusion studies have only been performed in a few patients with the syndrome (Donowitz & Binder, 1975; Davis et al, 1980). Both studies showed diminished sodium and water absorption and chloride secretion in the jejunum. Similar results were obtained in a study of serotonin effects on intestinal transport in the rabbit (Donowitz et al, 1977). In this study serotonin did not affect the active transport of glucose, adenylcyclase or Na-K-ATPase levels in the intestinal mucosa or intestinal histology. Thus, though this study confirmed that serotonin causes small intestinal secretion, the mechanism remains obscure, as none of the established secretory processes appeared to be involved.

Inhibition of serotonin synthesis (parachlorophenylalanine, α-methyldopa) or serotonin antagonism (methysergide, cyproheptadine) ameliorate the diarrhea in some patients with the carcinoid syndrome indicating that serotonin is indeed the main mediator of this symptom (Sjoerdsma et al, 1970). Interestingly, somatostatin infusion in two patients significantly reduced the diarrhea concomitantly with a reduction in urinary 5-HIAA excretion (Dharmsathaphorn et al, 1980; Davis et al, 1980). Davis et al also found an increased sodium and water absorption and a reversal of chloride secretion to absorption during somatostatin infusion. The striking decrease in urinary 5-HIAA excretion (70-80%) suggests that somatostatin inhibits the release of serotonin from the tumor. The symptomatic treatment of the diarrhea is best obtained with methysergide or cyproheptadine which have fewer side effects than the serotonin synthesis inhibitors (Grahame-Smith, 1974). In the Mayo Clinic's experience, however, the serotonin antagonists produce variable and unpredictable effects where only a minority of patients have claimed symptomatic improvements (Davis et al 1973). Although not studied in a systematic fashion, it is likely that the usual antimotility drugs (Codeine phosphate, Lomotil or Loperamide) may be more effective against the diarrhea.

Heart Disease - Fibrosis:

The cardiac lesions associated with the carcinoid syndrome are pathognomonic and are seen in about 50% of patients with usually advanced disease. The lesions called the 'carcinoid plaque' are usually restricted to the right side of the heart and involve the tricuspid and pulmonary valve. The unilateral involvement is thought to be due to inactivation of a mediator in the pulmonary circulation. The carcinoid plaques are white lesions in the endocardium with normal overlying endothelium. The lesions consist of smooth muscle cells in a stroma with abundant collagen and microfibrils, but devoid of elastic fibers (Amoury, 1970; Ferrans & Roberts, 1976). The plaques are thought to result from a superficial endocardial injury as the plaques do not involve deeper layers of the endocardium. The fibrosis may cause stenosis of the tricuspid and pulmonary valve and valve insufficiency with pulmonary stenosis and tricuspid regurgitation.

The carcinoid tumor may also produce a local intense fibrosis in tissues surrounding the tumor such as the mesentery, retroperitoneum and bladder (Bates & Clark, 1963; Hale & Lane-Mitchell, 1964; House & Herman, 1965; Grahame-Smith, 1972). The fibrotic reaction may cause obstruction of the intestine, involve the lymphatics and lymph nodes to cause chylous ascites or involve the blood supply to cause small bowel ischemia.

A probably unusual fibrotic feature is Peyronie's disease, which has been described in two patients with the carcinoid syndrome (Bivens et al, 1973). The authors suggested that patients presenting with Peyronie's disease should have determined urinary 5-HIAA excretion!

The chemical mediator of the fibrosis is not identified. Both serotonin and bradykinin increase capillary permeability and stimulate collagen synthesis in fibroblast cultures. It is interesting that the serotonin antagonist methysergide which contains an indole ring may cause retroperitoneal fibrosis whereas cyproheptadine without this molecular

structure, does not. Further, schistosomas have a high capacity for serotonin production (Bennett et al, 1969) and severe fibrosis in schistosomiasis is well recognised. These findings would tend to implicate serotonin or a degradation product as the prime suspect.

It is noteworthy, however, that the cardiac lesions develop in an unpredictable manner. Roberts & Sjoerdsma (1964) and Grahame-Smith (1972) have followed large series of patients with the carcinoid syndrome and found no significant difference in the urinary excretion of 5-HIAA in patients with carcinoid heart disease and those without.

Pellagra

Pellagra has been observed in a few patients with usually advanced carcinoid syndrome who presented with classical skin lesion that cleared on niacin supplementation (Bridges et al 1957; Thorson et al, 1958; Bean & Fusaro, 1968; Castillo & Lynch, 1972). The niacin deficency develops when these patients divert most of the available precusor, tryptophan, to serotonin synthesis. The skin lesions are often bilateral, hyperpigmentated with sharp margins and are usually seen in sun-exposed areas.

Myopathy

Myopathy is another unusual feature of the carcinoid syndrome and so far has only been described in two patients (Barry et al, 1974; Swash et al, 1975). Both patients had a marked atrophy of type II muscle fibers. Serotonin infusion has been shown to cause muscle weakness in animal experiments, but atrophy of type II fibers has not been observed (Patten et al, 1974; O'Steen et al, 1976). Cyproheptadine improved muscle strength in both patients.

Diagnosis and treatment

As long as the carcinoid tumors in the gastrointestinal tract are small and asymptomatic they most often remain undiscovered or are encountered as incidental findings during abdominal surgery for other reasons. The primary tumors tend to invade the submucosal layers and spread towards the serosa whereas the mucosa often remains intact. Thus, gastrointestinal bleeding is a rare finding in carcinoid tumors. When the tumors reach a certain size (> 1 cm) intusussception or obstruction may result and a barium study may show a polypoid filling defect. If the tumor has produced a local fibrotic reaction the small bowel lumen may appear narrow and the loop may be kinked or retracted. Some radiologists consider these findings typical for carcinoid tumors (Boijsen et al, 1974; Balthazar, 1978) but other diseases that cause mesenteric fibrosis such as retractile mesenteritis may produce a similar sign (Gold & Redman, 1972; Seigel et al, 1980). A previous claim that intestinal carcinoid tumors have a characteristic angiographic picture (Boijsen et al, 1974) could not be substantiated in a recent study (Seigel et al, 1980). Thus, in most cases, an UGI series is sufficient to demonstrate the localization of the lesion, but is not diagnostic unless the carcinoid syndrome is present.

In the rare instances where a carcinoid syndrome has developed from a gastrointestinal carcinoid tumor, the diagnosis is often obvious due to the unusual constellation of symptoms. Unfortunately, these patients have allways metastatic disease, primarily to lymph nodes and liver and often present with marked hepatomegaly. The diagnosis is confirmed by determination of urinary 5-HIAA excretion which is invariably elevated irrespective of the origin of primary tumor (Feldman, 1978). Bronchial and ovarian carcinoids, however, may produce the carcinoid syndrome before metastasizing as they release the mediators into the systemic circulation. Therefore, the primary tumor must be identified as this subgroup may be cured with resection of the tumor. In patients with gastrointestinal carcinoid tumors and liver metastases cure is rarely possible and the management of these patients is difficult. If the primary tumor is causing intestinal obstruction, surgical intervention is necessary with either resection of the obstructed segment and tumor or if resection is impossible due to mesenteric fibrosis, then the obstructed segment should be bypassed. In rare cases enucleation of liver metastases or hepatic lobectomy have been employed when only isolated metastases were present and a temporary cure or relief of the symptoms have ensued (Grahame-Smith, 1972). In most cases the liver metastases are multiple and widespread and, thus, not amenable for surgical resection.

In a few cases the carcinoid syndrome may arise from an intestinal primary associated with large lymph node metastases but without liver implants. Thus, if liver metastases are not found with the usual procedures (Liver-spleen scan, CT-scan or laparoscopy) a laparotomy is indicated and surgical resection of the tumor and lymphnodes should be attempted which may lead to symptomatic improval (Aranha & Greenlee, 1980).

If surgery is not feasible, chemotherapy should be considered. Unfortunately, the carcinoid tumors are relatively unresponsive to the chemotherapeutic agents so far employed. Moertel & Harley (1978) have tried two treatment modalities in 118 patients with the carcinoid syndrome. They observed a response rate of 32% with 5-FU and streptozotocin and 29% with streptozotocin and cyclophosphamide. A similar response rate was found by Chernicoff et al (1979) with 5-FU and streptozotocin in a small series of patients.

Survival

In Berge & Linell's autopsy study (1976) it was apparent that the presence of carcinoid tumors with or without metastases, but unassociated with the carcinoid syndrome did not influence survival. The mean age of those dying with a carcinoid tumor was not different from the mean age of those without a tumor. However, if the carcinoid syndrome is present, the survival rate is definitely shortened. In Davis et al (1973) series the median life span from the first history of flushing was 38 months with 25% still alive after 6 years. In most cases the cause of death is carcinomatosis per se but in some cases cardiac involvement with heart failure or massive mesenteric infarction due to fibrotic encroachment of the mesenteric vessels were the primary causes of death.

Summary

The advances in our knowledge of the carcinoid spectrum have mainly come from basic morphologic studies that have delineated the diffuse endocrine system and classified the cells within this system from which carcinoid tumors arise. The chemical mediators and their pathophysiologic role in the carcinoid syndrome are still incompletely defined and a rational pharmacological approach to the symptomatic treatment must await further development in this area. When the diagnosis of the carcinoid syndrome is made the disease is often too far advanced for curative therapy and it is doubtful that detection at a stage prior to liver metastases will be possible. Lastly, as with other gastrointestinal tumors, effective chemotherapy remains to be developed.

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Bean, 1958