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A Clinicopathologic Study

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With dedication to my wife Joyce and to my sons
Malcolm, Peter, Ian, and Anthony

Foreword

The quest to solve the mysteries of cancer has led to an accumulation of comprehensive information about the natures of many tumors. Yet scientific information about carcinoid tumors, a unique, infrequent type of neoplasm, is limited. The objective of the detailed study in this monograph is to elucidate the occurrence, the course of events, and the therapeutic responses of these tumors.

Skilled as an internist, a surgeon, and a scientist, Dr. Marks has thoroughly analyzed an unprecedented series of cases from our teaching institutions. The clinical, pathological, and therapeutic information should be of inestimable value as the definitive reference for clinicians, pathologists, and oncologists on the subject of carcinoid tumors.

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October 31, 1978

Preface

In 1978, English-speaking surgeons celebrated the 250th anniversary of the birth of John Hunter. Hunter was a key force in creating the scientific background of surgery and in fusing laboratory investigation with clinical study. It was he who wrote to Edward Jenner, "Why think? Why not try the experiment? " The product of the Hunterian tradition—the modern surgeon—has well been described as "a physician who is condemned to operate." The operation itself is merely one aspect of a surgeon's total involvement with a patient. The surgeon must also consider the pathology of the patient's disease, the existing investigations, and the patient's psychological and physiological responses to both the illness and surgery.

In this monograph, Charles Marks, with his wide background of surgical training in South Africa, the United Kingdom, and the U.S.A., demonstrates that he is a worthy Hunterian. He takes an uncommon, fascinating tumor and, drawing upon his broad clinical experience with 172 patients who have this condition at the Charity and the Veterans Administration Hospitals in New Orleans, paints a broad canvas for us. We are taken through the historical background of the disease, its biochemical peculiarities and markers, its pathology (from naked eye appearance to electron microscopy), and its relation to other cancers and multiple endocrine abnormalities. Careful consideration of pathology provides a useful guide to both treatment and prognosis. The encouraging results of the treatment of liver metastases and the development of specific drugs to combat the malign effects of the carcinoid syndrome follow logically from Dr. Marks' deep understanding of the pathological and biochemical effects of carcinoid tumors.

Other physicians, whose experience of this disease is confined to

the occasional cases which occur in their own practice, will be grateful to Dr. Marks who so happily blends art and science in this beautiful monograph.

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London, 1978

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Chapter 1

Introduction

From 1948 to 1971, 172 patients with carcinoid tumors were seen at Charity Hospital and Veterans Administration Hospital in New Orleans. One hundred thirty-five patients presented with carcinoids of the gastrointestinal tract. Thirteen patients represented a distinct group of carcinoid-islet cell tumors of the duodenum that justify distinct categorization, and 24 patients had bronchial adenomas of the carcinoid type.

In order to determine the natural history of carcinoid tumors at specific sites, the carcinoids were grouped according to location and mode of discovery. Table 1 compares our experience with the collected cases in the world. We found no patients with carcinoids of the esophagus, gall bladder, Meckel's diverticulum, pancreas, or ovary.

Attention was directed to the data of 106 clinical patients with gastrointestinal carcinoids. The clinical features, mode of diagnosis, treatment, pathologic features, and the presence or absence of coexisting disease were analyzed. Twenty-nine carcinoid tumors of the gastrointestinal tract represented incidental findings at autopsy and had produced no clinical symptoms. These cases were included only when pathologic features or the presence of coexisting disease were considered (Table 2).

The carcinoid tumors of the gastrointestinal tract were categorized according to size under one of three headings:

1. less than 1 cm
2. 1 to 2 cm
3. 2 cm or larger

Table 1. Carcinoid Tumors

Site	Collected Cases	Present Series
Esophagus	1	0
Bronchus	1% of Primary Lung Tumors	24
Stomach	98	10 (12 conventional)
Duodenum	135	25 (13 carcinoid-islet cells)
Jejunoileum	1,032	37
Meckel's diverticulum	46	0
Appendix	1,686	29
Colon	94	10
Rectum	706	37
Pancreas	2	0
Biliary tract	10	0
Ovary	34	0

Table 2. Location and Method of Discovery

Location	Clincial	Autopsy	Total
Bronchus	20	4	24
Stomach	8	2	10
Duodenum	21	4	25
Jejunoileum	18	19	37
Colon	8	2	10
Rectum	37	0	37
Appendix	27	2	29
Total	139	33	172

The appropriate size of tumors was obtained from the description recorded by clinicians, surgeons, or pathologists. The definition of size appeared important and a search was made for correlation between tumor size, the presence of symptoms, and extent of the disease process. Follow-up information was available in 102 of the 106 clinical patients and was provided by outpatient clinic reports or tumor registries (Morgan, Marks and Hearn, 1974).

Analysis of the 13 patients with carcinoid-islet cell tumors of the duodenum draws heavily on the previously published reports of this series of cases. Significant clinical differences justify consideration of this group within a separate and distinctive category.

The 24 patients with bronchial carcinoid tumors represented 86% of all the bronchial adenomas seen during this time; 3 (11%) were cylindromatous and 1 (3%) was a mucoepidermoid tumor. During this period 4553 cases of primary bronchogenic tumors were seen at these institutions. Bronchial adenoma represented 0.6% of all primary lung tumors. This study of the natural history of bronchial carcinoids reviews clinical symptoms and signs as well as radiologic and bronchoscopic findings. The presence of associated disease and the relationship of bronchial carcinoids to the polyendocrine syndrome is reviewed in the light of our experience.

If bronchial carcinoids are excluded, the total world collected series of carcinoid tumors accounts for less than 4000 cases (Table 1). Comparison between our institutional experience and the world experience is summarized in Figure 1.

The carcinoid tumor is generally considered to be a neoplasm that contains argentaffin cells derived from the Kulchitsky cells of the small intestine. Although tumors arising from sites other than the small intestines have been reported with clinical and biochemical findings previously associated with this classical definition of carcinoid tumors, they lacked argentaffin characteristics.

The classification of carcinoid tumors based on their origin from differing embryologic divisions of the primitive gut delineates as follows (see Table 3):

1. differences in histologic structure
2. variations in histochemical reaction
3. association with the carcinoid syndrome

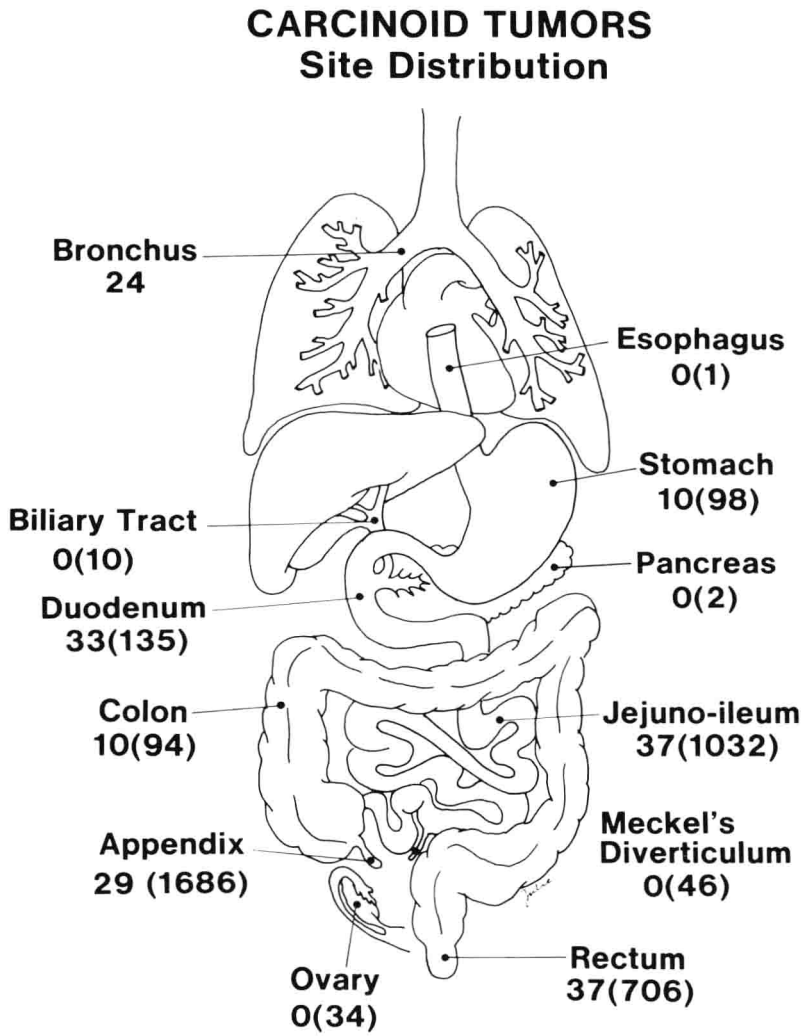

Fig. 1: Site distribution of carcinoid tumors. Figures in parentheses represent collected world series.

Table 3. Correlative Features of Carcinoid Tumors Based on Embryologic Derivation.
Predominant Features of Carcinoids in Relation to Primary Growth Sites

	Foregut	Midgut	Hindgut
Histology Silver imp.	B type argyrophil and nonreactive	A type argentaffin	Mixed type nonreactive
Biochemistry	5 HTP, tumor Serum, urine 5 HT, urine Histamine Serum, urine 5 HIAA, urine	5 HT, tumor Serum, urine 5 HIAA, urine	
Secretory Granules EM	Round, variably dense	Pleomorphic uniformly dense	Round, variably dense
Clinical	Bright red, Geographic Pattern	Mixed cyanosis Erythema	

NOTE: 135 carcinoid tumors of gastrointestinal tract L.S.U. affiliated hospitals.

4. changes in serum and urinary components of the tryptophan cycle
5. differences in the probability of metastases

Review of the Literature

Merling reported a case of primary carcinoma of the appendix in 1838; his description of the lesion is generally accepted as the first reference to a carcinoid of this organ. Carcinoma of the appendix is a rare condition, and it is now generally known that carcinoids represent the commonest tumors of the appendix. In 1867 Langhans described the first documented case of an ileal carcinoid, describing it as a "drusenpolyp." In 1882 Beger reported details of an adenocar-

cinoma of the appendix, thus providing microscopic information that, retrospectively, indicates that the lesion was a carcinoid.

In 1888 Lubarsch described two autopsy cases and complemented the gross study of the intestinal tumors with histologic examination. The first case demonstrated two small tumors situated in the ileum. In the second case, he described six small tumors in the lower ileum of a 52-year-old male. He described each of these tumors as small nodules of whitish tissue situated in the submucosa and involving the muscularis. The lesions were composed of nests and strands of epithelial cells arranged in a fashion quite unlike the conventional cylindrical arrangement of intestinal mucosal cells. Serial sections through the tumors demonstrated that these epithelial nests and strands were connected with the crypts of Lieberkühn. He considered that these tumors represented an outgrowth from the glands of the intestinal mucosa. The cells were arranged in a pseudoglandular pattern with small spaces within the cell nests arranged radially around an apparent glandular lumen. The presence of pink-staining amorphous material in the clear spaces led Lubarsch to conclude that these spaces were not lumina but probably vacuoles caused by cell necrosis. Although Lubarsch described his cases as primary carcinomata of the ileum, it is apparent that he provided a classic description of carcinoids of the ileum characterized by:

1. Multiplicity of the tumors.
2. Absence of a true glandular structure.
3. The tumors were of epithelial origin and traceable to the crypts of Lieberkühn.
4. Absence of metastases.

The apparent benignity of these lesions was questioned by Ransom who, in 1890, described a patient with a small tumor in the ileum that had invaded beyond the peritoneal covering into the mesentery. The microscopic appearance resembled that described by Lubarsch, except that there were multiple secondary tumors in the liver identical in histologic structure with the tumor in the ileum. Ransom stressed that the mesenteric lymph nodes were free of metastases. As there was no other primary neoplasm anywhere in the body, it was apparent that these lesions could metastasize.