CARCINOID TUMORS: A REPORT OF 38 CASES*

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THE UNUSUAL QUALITIES of carcinoid tumors have served to attract an interest in them out of proportion to their numbers. Earlier writers gave attention to their rarity, their obscure pathogenesis and their altered behavior in different portions of the gastro-intestinal tract. Recent studies have emphasized the combination of benign and malignant characteristics which is perhaps the most unusual quality of these tumors. After the report of Oberndorfer, in 1907,[48] it was generally accepted that carcinoids were benign tumors. Later it was gradually realized that some carcinoids were certainly malignant, but the remainder—although histologically identical—were thought of as benign. Various authors have resolved this inconsistency by stating that all carcinoids are essentially malignant; they have concluded that these tumors usually grow very slowly, but that all of them would become malignant if given time enough.[6, 9, 10, 16, 17, 22, 25, 26, 33, 37, 52, 57, 61] This concept has been accepted and stressed in every recent report.

From the viewpoint of the patient and his physician, the presence or absence of malignancy in a tumor would seem to be its most important property. In this respect, carcinoid tumors still present an unsolved problem. This uncertainty is due in part to the nature of the tumors and in part to their relative scarcity. In order to increase the material available for study, these 38 cases are reported from the files of the University Hospitals of Cleveland from January 1, 1932, to September 1, 1951.

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HISTORIC RÉSUMÉ

Although Langhans[32] had described in 1867 an unusual polyp of the ileum which was probably a carcinoid, Lubarsch[34] is credited with separating these tumors as an entity. In 1888 he reported two cases of multiple tumors of the ileum which differed from adenocarcinomas because of cellular dissimilarity and a lesser tendency to metastasize. Lubarsch called these tumors "primary carcinomas of the ileum" and believed that they originated from epithelial cells in the crypts of Lieberkühn. The first authentic case of carcinoid of the appendix was reported by Beger in 1882.[5]

PATHOGENESIS

From the time of the earliest reports it has been recognized that carcinoid tumors are histologically distinctive, but although much intensive work has been done, a satisfactory theory of histogenesis has yet to be generally accepted. Before the studies of Masson,[38-41] which simplified the problem, many cell types from all germ layers, as well as several embryonic anomalies, were implicated in the origin of carcinoids. In brief, these tumors have been regarded as true epithelial carcinomas, as basal cell carcinomas analagous to basal cell carcinomas of the skin, as ectopic pancreatic tissue, as tumors of the sympathetic nervous

system, and as any of several fetal maldevelopments. In 1914, using silver impregnation technics, Gosset and Masson[24] demonstrated that many carcinoid cells contain intracytoplasmic granules which stain black with silver, and further, that the so-called Kulschitsky cells of the intestinal epithelium contain identical argentaffin granules. These cells are normally present in small numbers, situated in the bases of the crypts of Lieberkühn, throughout the gastro-intestinal tract from the cardia to the anus. From these and later studies of Masson and others, it seems certain that carcinoid tumors arise from these cells; however, the origin, nature and function of normal argentaffin cells are not definitely known. Masson concluded that they are neuro-endocrine; he believed that carcinoids result from autonomous proliferation of argentaffin cells which, after migrating from the mucosa to the submucosa, have invaded neurons of the plexus of Auerbach. Later investigators have been unable to agree with these conclusions[14] and, while the work of Masson has resulted in considerable elucidation of the problem, the precise pathogenesis of carcinoid tumors is still unknown. The subject has been reviewed by Forbus[21] (1925), Cooke[12] (1931), and Cruickshank and Cunningham[13] (1949).

INCIDENCE AND LOCATION

Normal argentaffin cells are more numerous in the appendix than in any other portion of the gastro-intestinal tract,[42] and all reports agree that the appendix is the most common site of origin of carcinoid tumors. They have been found in 0.2 to 0.5 per cent of large series of surgically removed appendices.[26, 53, 60, 71] In this series, exactly half (19) of the carcinoid tumors were situated in the appendix (Table I); 18 (95 per cent) of these were found in surgical specimens, the other being discovered incidentally at autopsy. During the period covered by this report, approximately 12,000 surgically removed appendices were examined; the incidence of carcinoid tumors was thus approximately 0.16 per cent.

Twenty-three surgical specimens contained carcinoids; thus, 78 per cent of carcinoid tumors occurring in surgical specimens were in the appendix. Fifteen other carcinoids from all sites of origin were found in 7553 autopsies during the report period (0.2 per cent incidence), but only one of these was in the appendix. This discrepancy between the most common site of origin in surgical and in autopsy material, which has been noted by others,[25, 52] may be due to (1) early obstruction of the appendiceal lumen by a small tumor resulting in inflammation and consequent surgical removal, (2) the frequency of appendectomy compared to resections of other portions of the gastro-intestinal tract, leading to the discovery of asymptomatic tumors, and (3) the relatively cursory examination given to the appendix at autopsy in contrast to interest displayed in it as a surgical specimen.

TABLE I.—*Location of Carcinoid Tumors, Author's Series.*

Primary Site	Number	Multiple Primary	Metastasis	Associated Malignancy
Duodenum	1	0	0	0
Jejunum	2	1	1	0
Ileum	11	1	3	6
Appendix	19	0	0	2
Rectum	5	0	1	0

The terminal ileum is the most common site of origin of extra-appendiceal carcinoid tumors in both surgical and autopsy specimens.[2, 12, 18, 52] In various collective reviews, 85 to 96 per cent of carcinoid tumors were found in the vicinity of the ileocecal valve, i.e., in the appendix, cecum, or terminal ileum.[2, 12, 55] The ratio of appendiceal to ileal carcinoids ranged from two to one up to ten to one.[18, 25] In this series, 11 of 19 extra-appendiceal carcinoids (58 per cent) were in the ileum

(Table I). The remainder were situated in the duodenum, jejunum and rectum. In addition to the above sites, carcinoid tumors have been described occasionally in the stomach, gallbladder, ampulla of Vater, cecum, colon, Meckel's diverticulum, and teratoma of the ovary.[3, 46, 52]

PATHOLOGY

In the appendix, carcinoids may vary in size from microscopic lesions to growths 2 cm. in diameter, which usually appear as bulbous swellings of the tip and are often thought to be fecaliths at the operating table. Less well-developed tumors may be discovered on gross examination of a cross section of the appendix, and are usually described as a well-defined area of firm, homogeneous, yellow or yellowish-gray tissue which has obliterated the distal portion of the lumen. The tumor is situated primarily in the submucosa and the mucosal and muscular layers are usually grossly intact. In this series, the location of the appendiceal tumor was specified in 12 cases; in ten of these the tumor was located at or near the tip. The tumor was grossly apparent in nine of 19 cases, usually as a bulbous enlargement of the tip.

Extra-appendiceal carcinoid tumors characteristically appear as one or more small, firm, yellow or gray submucosal nodules. The tumor usually projects into the intestinal lumen as a sessile or polypoid mass, but rarely causes intestinal obstruction by virtue of its mass alone except when situated at the ileocecal valve. Carcinoid tumors in all situations are usually accompanied by moderate to marked fibrous tissue hyperplasia; this occasionally results in the formation of fibrous annular constrictions of the intestine. In contrast to adenocarcinomas, the mucosa overlying carcinoids is nearly always intact; because of this, gastro-intestinal bleeding is rarely a symptom except in carcinoids of the rectum. Superficial mucosal ulceration has been noticed in about one-fourth of the reported cases of rectal carcinoid, and occurred in one of five cases in this series.

The first two cases of carcinoid of the ileum reported by Lubarsch were multicentric in origin; this resulted in a general impression that most intestinal carcinoids arose from multiple sites. With the passage of time, less and less emphasis is being placed upon this characteristic. Various surveys of the literature indicate that 18 to 36 per cent of small intestinal carcinoids arise from multiple foci,[2, 12, 17, 52] but multiple carcinoids of the appendix and large intestine are very unusual.[27, 63] In this series, two (14 per cent) of 14 small intestinal carcinoids were multiple. In one case, that of a 50-year-old man dying of congestive heart failure, 12 benign carcinoids of the ileum were an incidental finding at autopsy. In the other case, a 47-year-old woman with chronic small intestinal obstruction was found to have two malignant carcinoids of the jejunum; the larger tumor, which measured 2 cm. in diameter, had caused a jejuno-jejunal intussusception.

Carcinoid tumors may invade into or through the muscular or serosal layers of the bowel wall. When the serosa is involved, it is usually retracted or dimpled. Further direct extension into the adjacent mesentery results in the development of masses of fibrous tissue which may be several times larger than the primary tumor; these masses are often grossly mistaken for lymph nodes, but on microscopic examination are found to be comprised of tumor cells embedded in an abundant fibrous tissue stroma. These extra-serosal tumor masses frequently result in the development of adhesions between contiguous loops of intestine; by all accounts this is the most common cause of small intestinal obstruction due to carcinoid tumors.[45, 52]

Microscopically, carcinoids consist of nests, columns or masses of small, uniform,

round or polygonal epithelial cells lying in a fibrous stroma. The prominent nuclei are usually round but may be oval; the nuclear membrane is well-defined and there is abundant finely-stippled chromatin which is deeply basophilic. The cytoplasm is pale, indistinct, and acidophilic and contains numerous acidophilic granules whose argentaffin property has been mentioned. The tumor cells are sometimes grouped around a space in such a manner as to simulate gland or rosette formation; these central spaces often contain an amorphous acidophilic material. Both solid and glandular cell arrangements may be found in the same tumor, but there is usually a preponderance of one type. The fibrous or hyaline connective tissue stroma is variable in amount but is usually prominent. A pseudocapsule is often formed by condensation of smooth muscle fibers at the periphery of the tumor.

Some carcinoid tumors, especially those of the rectum, do not possess argentaffinity, presumably because of the absence from the granules of some substance which is necessary for the reduction of silver salts.[23, 68] Moreover, cells in other situations, such as the beta cells of the pancreatic islets, are also argentaffin. For these reasons, the term "argentaffin tumor," which is often applied to carcinoids, should be abandoned as it is neither inclusive nor specific.

The term "carcinoid" itself is deficient. Oberndorfer suggested it in 1907, believing that these "carcinoma-like" tumors were invariably benign. Since Ransom's report[56] of a case of carcinoid of the ileum with metastases in 1890, more than 400 cases with metastases have been reported,[58] and it is obvious that many, if not all, carcinoids are actually or potentially malignant. It is now customary to apply the term "malignant carcinoid" to tumors with proved metastases and to call the remainder "benign carcinoids"; this convention is followed in the present report. A group at the Mayo Clinic has suggested the name "adenocarcinoma grade one (carcinoid)" to emphasize their belief that all carcinoids are malignant but yet distinctive from ordinary adenocarcinomas;[17, 18, 26] this term has not gained wide acceptance.

MALIGNANCY

In considering the question of malignancy, the unusual invasive characteristic of carcinoids must be appreciated. Presumably the tumor always originates in the submucosal layer of the gastro-intestinal tract[14, 40, 41] and may exist there for a very long period without invading adjacent tissue layers. It is not unusual to find microscopic lesions and gross tumors measuring up to 1 cm. in diameter which are confined entirely to the submucosa. On the other hand, a considerable number (possibly the majority) of carcinoids eventually invade the adjacent muscularis after lying dormant in the submucosa for variable periods of time. Evidence of this invasion is first seen microscopically as a scattering of small nests of tumor cells in the zone of the muscularis nearest to the submucosa. This centrifugal infiltration proceeds through the muscular layer into and occasionally through the serosa. Such an involvement of all tissue layers is usually associated with larger tumors, 1 cm. or more in diameter, but Gaspar concluded that even the smallest nests of cells have the ability to infiltrate the muscularis. Table II indicates that nine of 19 appendiceal tumors in this series were large enough to be grossly apparent; in eight of these nine cases there was microscopic (and possibly gross) involvement of the muscularis; in six cases there was also involvement of the serosa; and in one case there was also infiltration of the mesenteric fat. On the other hand, microscopic invasion of the muscularis was found in only three of ten tumors not large

enough to attract attention grossly and in one of these cases there was gross obliteration of the appendiceal lumen. The same observation was made in tumors of the small intestine and rectum (Tables III and IV). Nine tumors of the small intestine which were confined entirely to the submucosa averaged 0.44 cm. in diameter, while five tumors which had invaded at least the muscularis averaged 1.24 cm.

sional hematogenous spread is indicated by the discovery of metastases in virtually every organ of the body; moreover, tumor emboli are sometimes seen in blood vessels.

The microscopic appearance of a carcinoid tumor tends to complicate rather than facilitate the appraisal of its malignancy. Abnormal mitoses and other atypical cell forms are often noted in tumors which must

TABLE II.—*Carcinoid Tumors of the Appendix.*

Case No.	Age	Sex	Gross Tumor	Obliteration of Lumen	Involvement Musc.	Serosa	Mes.	Remarks
1	12	F	x	x	x			Acute appendicitis
2	26	F	x		x	x		Incidental with hysterectomy
3	45	F						Incidental with hysterectomy
4	15	F	x	x	x	x		Chronic recurrent appendicitis
5	51	F						Incidental with hysterectomy
6	47	F	x		x	x		Incidental with hysterectomy
7	57	M	x		x			Incidental at autopsy
8	22	M	x	x				Acute appendicitis
9	20	F		x				Chronic recurrent appendicitis
10	35	F						Incidental with hysterectomy
11	36	F	x	x	x	x		Chronic recurrent appendicitis
12	46	F			x			Incidental with hysterectomy
13	38	F		x				Incidental with hysterectomy
14	21	F	x	x	x	x		Acute appendicitis
15	31	F			x			Incidental with ovariectomy
16	26	M		x				Acute appendicitis
17	26	F	x	x	x	x	x	Chronic recurrent appendicitis
18	45	F		x	x			Incidental with hysterectomy
19	30	F						Incidental with hysterectomy for squamous cell carcinoma of cervix

These findings seem to indicate a positive correlation between tumor size and invasiveness; they may lend support to the contention that all carcinoid tumors will become frankly malignant if given time enough.

At present, however, local invasiveness is not usually regarded as a criterion of malignancy in carcinoids. Tumors are classified as malignant only on the basis of proved metastasis. Metastases usually occur in the regional lymph nodes, in the mesenteric fat and, to a lesser extent, in the liver. Tumor cells are often identified in the lymphatic vessels of malignant primary tumors and of the regional lymph nodes; unquestionably, the principle route of dissemination is via the lymphatics. Occa-

be classified as benign on the basis of their gross appearance and absent metastases. Conversely, in tumors which are obviously malignant, and even in metastatic foci, the cells may exhibit none of the usual histologic criteria of malignancy.

It is characteristic of carcinoids that the location of the primary tumor appears to be a significant factor in the development of metastases. Malignant carcinoids of the appendix are rare, only 23 cases having been reported,[1, 16, 26, 33, 58] while malignant tumors of extra-appendiceal origin are comparatively common. The recent statistics of Pearson and Fitzgerald[52] are typical; in a review of 140 consecutive cases they found no malignant tumors in 98 appendiceal carcinoids and 16 malignant tumors in 42

extra-appendiceal carcinoids. In the series reported here, there were no malignant tumors in 19 appendiceal carcinoids and five malignant tumors in 19 extra-appendiceal carcinoids (Table I). Every author is agreed that appendiceal and extra-appendiceal carcinoids are morphologically identical; moreover, those few carcinoids of the appendix which did metastasize were similar in every respect to malignant carcinoids from other locations. Mörl and others believe that appendiceal carcinoids are as malignant as any; they suggest that in most cases obstruction of the appendiceal lumen by a small tumor results in the development of inflammation and consequent appendectomy before metastases have occurred.[25, 47, 52]

Because the clinical course, prognosis and problems of treatment of carcinoid tumors tend to vary significantly according to their site of origin, the clinical data of this report are divided into three sections based upon the location of the tumor.

CARCINOID TUMORS OF THE APPENDIX

These tumors are usually discovered in young people. In a series of 186 cases Simon[63] found that two-thirds were under 30 years of age. The average age at which appendiceal carcinoids were discovered was 24 years, 25 years, 29.5 years, and 30 years in four surveys.[25, 35, 50, 55] In the series reported here, the youngest patient was 12, the oldest was 51, and the average was 33.1 years (Table II). In eight patients who displayed symptoms before appendectomy, the average age was 22.2 years with a range of 12 to 36 years.

In four large series, the percentage of tumors occurring in females ranged from 65 to 82 per cent.[12] Of the 19 cases reported here, 16 (84 per cent) were in females. Two males, 22 and 26 years old, had acute suppurative appendicitis, and the third male case was discovered incidentally at autopsy. The preponderance of females may be partially explained by the fact that ten tumors were found in asymptomatic appendices removed incidentally during gynecologic operations.

In this series, four (21 per cent) of the appendiceal tumors were associated with (and were probably responsible for) typical attacks of acute appendicitis. Four other cases presented with a syndrome of right lower abdominal pain, often accompanied by nausea or vomiting, occurring intermittently over a period of months or years; the diagnosis in these cases was chronic recurrent appendicitis. So far as could be determined, the remaining 11 cases were asymptomatic.

Table II shows that the appendiceal lumen was occluded or obliterated by tumor cells and fibrous tissue in eight of eight symptomatic cases, but in only two of 11 asymptomatic cases. There was a similar positive correlation between tumor size and symptoms. These observations agree with the general conclusion that appendiceal carcinoids produce symptoms by obstructing the lumen.

To make a preoperative diagnosis of carcinoid in a case of acute appendicitis is obviously impossible, but the diagnosis should be thought of in the case of a young woman with symptoms of chronic recurrent appendicitis.[12, 16, 33, 38, 39, 70]

All of the patients in this series were treated by appendectomy. The follow-up is admittedly inadequate, but no sequellae have been reported except in one case. Because of its "semi-malignancy," this case merits special attention.

Case 17.—A 26-year-old white female was admitted July 17, 1949, with the chief complaints of "tipped uterus and trouble with my appendix." Her uterus had been retroverted persistently since pregnancy 6 years previously, and there was a 5-year history of intermittent right lower abdominal pain accompanied by nausea. On physical examination the uterus was retroverted and there was slight direct tenderness at McBurney's point. The following day uterine suspension and

appendectomy were performed. The operating surgeon noted that "the appendix was quite bound down to the cecum with many veil-like adhesions." The patient was discharged on the eighth postoperative day after an uneventful convalesence.

At pathologic examination the appendix measured 6.0 cm. in length and 0.5 cm. in diameter. The distal one-third was dilated to a diameter of 1.3 cm., and in this portion the lumen was occluded by pale yellow-gray, firm, homogeneous tissue. Microscopic examination revealed numerous nests of typical carcinoid cells with occasional gland formation in the submucosa, muscularis, serosa and mesenteric fat. Tumor cells extended to the edge of the meso-appendix, indicating incomplete excision of the tumor.

The patient has been followed casually for 26 months. During this period her weight has decreased from 105 to 102 pounds. Throughout the follow-up period she has had intermittent attacks of diarrhea, accompanied by cramp-like pains in the left lower abdomen. Thus far she has been reluctant to undergo a complete diagnostic study.

Comment. In this case the malignant propensity of the tumor was such that invasion of the mesentery had already occurred in a 26-year-old woman. It is unknown whether her present symptoms are due to possible metastases from the incompletely excised tumor. Malignant carcinoids and their metastases often grow very slowly, with the most insidious development of symptoms.

The tumor in the above case has been arbitrarily classified as benign because metastases were not demonstrated. Four reported appendiceal tumors, without metastases, were classified as malignant by their authors solely on the basis of microscopic infiltration of the mesenteric fat.[33, 58] In addition, Grimes and Bell[25] had a similar case which they classified as "possibly malignant." Regardless of present confusion in standards of malignancy, there can be no doubt that appendiceal carcinoids have a tendency to invade their mesenteries. In all cases where carcinoid is suspected the meso-appendix should be excised as widely as possible.

CARCINOID TUMORS OF THE SMALL INTESTINE

Carcinoid tumors of the small intestine, while much less numerous than those of the appendix, are more important to the clinician because of their malignant tendency. In every large series, the ileum has been the most common site of origin of malignant carcinoids.[2, 12, 52, 74] In a group of 68 malignant tumors collected from various authors, the distribution of the primary sites was as follows: stomach, one; jejunum, two; ileum, 39; small intestine (unspecified), nine; appendix, 14; and colon, three.[45] Carcinoids comprised 23 per cent of a large series of small intestinal malignant tumors.[17]

Carcinoid tumors of the small intestine are usually discovered in the fifth or sixth decade of life and there appears to be a slight preponderance of males. The average age of patients with small intestinal carcinoids was 54.9, 55, 57.5, and 58 years in four reviews.[2, 12, 25, 55] The preponderance of males was consistent in each series and averaged 58 per cent. In the series reported here, the youngest patient was 39, the oldest was 81, and the average was 52.7 years (Table III). There were eight males (57 per cent) and six females; however, all four malignant tumors occurred in females. These four patients averaged 54 years of age. In large collective reviews there has been no significant difference in age or sex between benign and malignant tumors.

Small intestinal carcinoids frequently produce symptoms; they were present in 17, 24 and 36 per cent of cases in three large collected series.[2, 12, 29] Almost invariably the symptoms are those of intestinal obstruction. Since carcinoids tend to grow from the submucosa toward the periphery of the bowel, obstruction resulting from occlusion of the intestinal lumen by a tumor mass is very unusual. In most cases obstruction has been caused by relatively small primary tumors which, by extending

through the bowel wall, have produced metastatic tumor masses on the serosa and adjacent mesentery. These have led to the formation of adhesions between contiguous loops of intestine, resulting in chronic partial obstruction or, less often, acute complete obstruction. Knuckling or kinking of the bowel is favored by contraction strictions of the bowel are occasional modes of obstruction.

Diarrhea and weight loss are other important symptoms of small intestinal carcinoids; presumably they are secondary to chronic partial obstruction and are observed more often in cases with malignant tumors.

TABLE III.—*Carcinoid Tumors of the Small Intestine.*

Case No.	Age	Sex	Location	Diameter	Involvement	Symptoms	Associated Malignancy
20	81	F	Ileum	0.5 cm.	Submucosa	None	Carcinoma of pancreas
21	49	M	Ileum	0.7 cm.	Submucosa	None	None
22	58	M	Jejunum	0.3 cm.	Submucosa	None	None
23	43	M	Ileum	0.7 cm.	Submucosa & muscularis	None	None
24	57	M	Ileum	0.2 cm.	Submucosa	None	Carcinoma of stomach
25	39	M	Ileum	0.4 cm.	Submucosa	None	Carcinoma of adrenal cortex
26	58	M	Ileum	0.4 cm.	Submucosa	None	Carcinoma of liver
27	69	F	Ileum	1.5 cm.	Submucosa, muscularis, serosa, mesentery, & regional lymph nodes	None	Carcinoma of breast; mastectomy 9 years previously
28	50	M	Ileum	0.2 to 1.5 cm. (12 tumors)	Submucosa	None	None
29	50	F	Ileum	2.0 cm.	Submucosa, muscularis, serosa, mesentery, and regional lymph nodes.	None	None
30*	47	F	Jejunum	1.0–2.0 cm. (2 tumors)	Submucosa, muscularis, serosa, mesentery, lymph nodes, liver.	Small int. obstruction, weight loss, diarrhea.	None
31	45	M	Ileum	0.4 cm.	Submucosa	None	Plasma cell myeloma
32	42	F	Duodenum	0.6 cm.	Submucosa	Epigastric pain, vomiting, diarrhea.	None
33	50	F	Ileum	1.0 cm.	Submucosa, muscularis, serosa, mesentery, lymph nodes, liver.	Small int. obstruction, weight loss.	None

*This case has been previously reported elsewhere.[64]

of the fibrous stroma of the mesenteric tumor masses. The implication that malignant tumors are more likely to produce symptoms, since only these tumors produce peritoneal implants, has been confirmed by data from several reports. In one series, 13 of 21 malignant tumors resulted in obstruction, but only seven of 94 benign tumors did so.[12] In another series, 19 of 33 malignant tumors and 15 of 46 benign tumors caused obstruction.[2] In a third series, obstruction was produced by four of nine malignant tumors while all 14 benign tumors were completely asymptomatic.[52]

Intussusception and fibrous annular con-

In this series of 14 small intestinal carcinoids, four tumors were malignant with metastases to the regional lymph nodes or farther. Two of these cases, with metastases to the regional lymph nodes only, were asymptomatic and were discovered incidentally at autopsy; one of these (Case 27) was the case of a 69-year-old woman dying of a ruptured arteriosclerotic aortic aneurysm, and the other (Case 29) was that of a 50-year-old woman with known hypertension who died of cerebral thrombosis. The two cases with metastases to the regional lymph nodes and to the liver were symptomatic and are reported in some detail below.

Case 30.* A 47-year-old colored woman was admitted December 14, 1946, with a history of intermittent epigastric cramps, nausea, vomiting and diarrhea during a 14-month period in which she had lost 40 pounds. These symptoms continued during her hospital stay. Physical examination, laboratory findings, and the results of various diagnostic procedures were consistent with the diagnosis of chronic partial obstruction of the small intestine. Four roentgen ray studies of the stomach and small intestine were not remarkable, but on the fifth examination the radiologist observed partial obstruction of the distal jejunum by "a point of narrowing 6 cm. in length which appeared to be kinked." At operation, on February 24, 1947, a jejuno-jejunal intussusception was discovered. The intussusceptum measured 25 cm. in length and a 2.0 cm. carcinoid tumor was situated at its head. A second, smaller tumor was noted 12 cm. proximally, and 3 large, firm lymph nodes measuring up to 2.0 cm. in diameter were found at the root of the mesentery. The liver appeared to be normal and was not biopsied. The intussusception was reduced and the involved intestine and mesentery were resected.

The pathologic diagnosis of the surgical specimen was "malignant carcinoid of small intestine with metastasis to mesentery and lymph nodes." All layers of the intestine were invaded or replaced by nests of typical carcinoid cells; tumor emboli were seen in vascular spaces. An argentaffin stain was positive.

As a result of intestinal perforation during an abdominal paracentesis, the patient died of peritonitis on the nineteenth postoperative day. At autopsy numerous enlarged lymph nodes were found at the root of the mesentery of the jejunum; at least five of these contained metastatic carcinoid on microscopic examination. Dispersed throughout the liver was several discrete, firm, yellow or yellowish-gray nodules measuring 0.2 or 0.3 cm. in diameter; these also were found to be metastatic carcinoid on microscopic examination.

Case 33. This 50-year-old woman had intermittent attacks of epigastric and periumbilical cramps, brought on by eating and relieved by belching, for 18 months before admission, during which period she had lost 30 pounds. Three days before admission, which was on November 15, 1950, obstruction evidently became complete and she was admitted complaining of abdominal cramps, vomiting and constipation. Examination on admission was consistent with a diagnosis of small intestinal obstruction. The patient was not critically ill and responded well to conservative therapy. By the seventh hospital day the tip of the Miller-Abbott tube, which lay in the ileum, had ceased to advance. A small amount of roentgen ray contrast medium introduced through the tube demonstrated a constriction of the ileum about 2.5 cm. in length and 0.3 cm. in diameter. At operation the same day, a fibrous annular constriction was found to have obstructed the ileum 24 inches above the ileocecal valve. At this site a tumor 1.0 cm. in diameter was situated in the intestinal wall at the mesenteric border. In the mesentery, 1 cm. from the intestinal lesion, was a solitary, firm, gray spherical mass 3.0 cm. in diameter. No other masses were evident in the mesentery or intestine, but the liver was studded with many small gray nodules averaging 0.4 cm. in diameter. A frozen section diagnosis of carcinoid was made during the operation, following which the involved segment of ileum and its mesentery were resected.

Microscopically the intestinal tumor, the mesenteric mass and the liver biopsy consisted of typical carcinoid cells, a few of which had formed acini. All layers of the intestine had been invaded or replaced by tumor. In the mesentery, tumor cells had invaded fat, lymphatics, lymphoid tissue and nerve sheaths.

The patient has been followed 11 months since operation; she is symptom-free and has gained 17 pounds.

Comment. This patient's favorable postoperative course in the presence of liver metastasis is not surprising. There is ample clinical evidence that metastases from carcinoids of the small intestine are often very slow in growing and, in fact, may regress after resection of the primary tumor.[11, 15, 18, 25, 44, 53, 54] The astonishing case reported by Mallory[36] is often cited. A patient was operated upon in 1913 for an obstructive carcinoid of the ileum; the involved segment was resected and an end-to-end anastomosis was done. At this time no attempt was made to remove a large retroperitoneal metastasis. At autopsy 20 years later, following death from lobar pneumonia, the retroperitoneal mass was found unchanged except for partial calcification. Two cases have been reported which survived for ten years each with inoperable metastases following resection

* This case has been previously reported.[64]

of the primary tumor.[25, 67] In a few cases there has been prolonged survival with no treatment, or only palliation. In one case an obstructing tumor at the ileocecal valve was by-passed with an ileocolostomy, while the primary tumor and its many widespread metastases were not removed because they were thought to be inoperable. When the patient died ten years later with an unrelated disease, no appreciable change in the tumor or its metastases was found at autopsy.[72] In a similar case the patient died of drowning five years after an ilecolostomy. At autopsy there was regression of the primary tumor and no further growth of the many hepatic metastases.[69]

These isolated reports should not encourage the belief that a carcinoid tumor of the small intestine can be judiciously neglected. In the series of Grimes and Bell,[25] six patients with inoperable tumors survived an average of 27 months; four patients in whom an entero-anastomosis could not be done survived an average of 12 months.

The treatment of choice is surgical excision. Benign tumors should be excised because of their known malignant potential and because they occasionally produce symptoms. Malignant carcinoids should always be resected wherever possible, together with as much of their metastatic spread as is feasible.[25, 28, 52] The reports mentioned above demonstrate that even the partial removal of a malignant tumor has been accompanied by prolongation of comfortable life for many years. Pearson and Fitzgerald[52] have recently emphasized the importance of frozen-section diagnosis of questionable lesions at operation. By ordinary surgical standards a metastatic nodule in the liver might lead to the conclusion that a primary tumor of the small intestine was inoperable, whereas resection of the primary and metastatic lesions, even in the liver, would be justified if the tumor were a carcinoid.

The accessibility and relatively slow growth of carcinoids of the small intestine should make them more amenable to surgical treatment than any other malignant tumor of the gastro-intestinal tract. As in any tumor, the prognosis is intimately related to the extent of malignant dissemination. Ariel[2] studied all of the cases of small intestinal carcinoid reported from 1930 to 1939 and concluded that the prognosis was generally good in cases which were diagnosed early; widespread metastases usually developed in cases which were diagnosed late, and in them the prognosis was not as good. Grimes and Bell emphasized the importance of early diagnosis and listed a symptom tetrad comprised of intermittent small bowel obstruction, abdominal pain, diarrhea and weight loss. Miller and Herrmann[45] described the typical patient as a middle-aged man or woman who complains of long-standing gaseous distention, bloating, peri-umbilical pain, audible borborygmi, occasional diarrhea, and progressive weight loss. In the same report they described a roentgen ray finding on the basis of which they diagnosed a case preoperatively, the only such case ever reported. With barium contrast roentgenograms they studied two cases of malignant carcinoid of the small intestine which had caused obstruction. In each case there was a small, irregular filling defect (the tumor) at the site of obstruction; there was also a sharp kinking or knuckling of the intestine at the same site. It is the coexistence of the small tumor shadow with the kinking of the bowel at the point of obstruction which is regarded as significant.

Radiation therapy of carcinoid tumors has been used in a few cases with equivocal results.[2, 4, 7, 52] Ariel reported a case which may have been benefited by radiation. The patient was found to have an abdominal mass two months after resection of a malignant carcinoid of the ileum. The mass was thought but not proved to be a

local recurrence, and an unspecified dose of radiation was given. Thirty months later the patient was entirely well and had gained 30 pounds; the abdominal mass had disappeared. Brown *et al.*[7] radiated lymph nodes left behind after a primary tumor was resected; the dosage was 500 r daily for six days. When the nodes were excised two months later the tumor cells showed no radiation effect.

routine physical examinations or proctoscopy. Symptoms, when present, usually included rectal bleeding in some form; other occasional symptoms were constipation, tenesmus and rectal pain.

Thirteen tumors, all benign, were incidental findings at autopsy or in surgical specimens excised for another reason. In general, the benign tumors measured less than 1 cm. in diameter, lay in the lower part of the rectum, and were covered by intact mucosa. Microscopically the tumors were usually confined to the submucosa; however, infiltration of other layers up to but not through the serosa was a common finding. There were multiple primary tumors in three cases, one of which was malignant.

TABLE IV.—*Carcinoid Tumors of the Rectum.*

Case No.	Age	Sex	Color	Size	Involvement	Symptoms
34	71	M	C	0.5 cm.	Submucosa	None
35	34	F	C	1.5 cm.	All intestinal layers, regional lymph nodes; paraduodenal lymph node.	Large intestinal obstruction; rectal bleeding; weight loss.
36	42	F	W	0.7 cm.	Submucosa	None
37	57	M	C	0.3 cm.	Submucosa	None
38	56	F	C	?	Submucosa	None

CARCINOID TUMORS OF THE RECTUM

As the site of origin of carcinoid tumors the rectum is exceeded in frequency only by the appendix and lower small intestine. A total of 69 rectal carcinoids have been reported or mentioned in medical literature;[27, 43, 52, 59, 61, 73] that the lesion is probably more common than this is indicated by the discovery of ten rectal carcinoids in a series of 813 gastro-intestinal tumors from patients of military age during World War II.[20] Five additional cases of carcinoid of the rectum, one of which was malignant, are reported here (Table IV).

Seventeen cases from the literature have been merely mentioned; further information about these tumors is unavailable, except that one case is said to have been malignant.[52] Of the remaining 52 cases, seven were malignant and 45 benign. The ages of the patients varied from 14 to 71 years, with an average in the sixth decade. There was no significant sex difference. The race of the patient was reported in 16 cases, of which seven were Negroes; four of the five cases reported here were in Negroes. About three-fourths of the tumors were asymptomatic and were discovered during

As reports of rectal carcinoids accumulate, it has become apparent that these tumors, in contrast to small intestinal carcinoids, are clinically either quite benign or else extremely malignant (Table V). In the malignant cases, metastases were usually far advanced when the patient was first seen, even though symptoms were, as a rule, present for a relatively short time. Symptoms referred to the primary tumor in six cases and to hepatic insufficiency resulting from metastases in two cases. Three primary malignant tumors were large, infiltrating annular masses; the other primary tumors were sessile or polypoid nodules measuring 1.0 to 3.0 cm. in diameter. Combined abdominoperineal resection of the rectum was done in three cases and a palliative colostomy was formed in two additional cases. None of the patients is

living. The average survival from the time of first consulting the physician is 12 months; the longest survival is 32 months.

The very malignant nature of some rectal carcinoids has led Rosser[59] to suggest that there may be two distinct varieties of these tumors: (1) a benign lesion which may infiltrate all layers of the intestine but is apparently halted permanently at the less than in adenocarcinoma. As the tumor enlarges the cells will eventually transgress their barriers." This concept stresses the importance of early diagnosis of "benign" rectal carcinoids. Virtually all of these tumors, benign and malignant, lay within easy reach of an examining finger.

Four of the five rectal carcinoids seen at the University Hospitals of Cleveland

TABLE V.—*Malignant Rectal Carcinoid Tumors.*

Author	Age–Sex	Primary Tumor	Metastases	Symptoms	Remarks
Siburg 1929	71–M	Pea-sized nodule near anus	Lymph nodes, liver, lung, veretbrae	Abdominal mass	Died suddenly soon after admission to hospital
Koch 1940	64–M	10 cm. annular tumor 3 cm. above anus.	Lymph nodes, bladder, liver	Constipation and tenesmus, one month	Colostomy; died 8 months
Pearson & Fitzgerald 1948	51–M	3 polypoid nodules of lower rectum	Lymph nodes, liver, pancreas, thyroid, kidney	Tarry stools of decreasing caliber, 6 weeks	Abdominal exploration only; died 30 months
Pearson & Fitzgerald 1948–49	45–F	Annular mass 14 cm. above anus	Lymph nodes, liver, kidney	Constipation, rectal bleeding, vomiting, 10 months	Colostomy; died 30 months
Pearson & Fitzgerald 1949		Case mentioned only; not described.			
Horn 1949	29–F	2 x 3 cm. nodule 1 cm. above anus	Lymph nodes, liver, lungs, spleen, pancreas, adrenal	Abdominal pain, vomiting, weight loss, constipation, 11 weeks	Biopsy only; died 3 months of hepatic insufficiency
Wilson 1949	57–M	3 cm. nodular tumor of lower rectum	One regional lymph node	Rectal bleeding	Combined resection of rectum; died 22 days of pulmonary embolism
Rosser 1951	52–F	6 cm. annular tumor 5 cm. above anus	Lymph nodes, liver	Rectal pain, constipation, dysuria, back pain, 2 months	Combined resection; perineal recurrence in 2 months; died 8 months
Foreman 1952	34–F	1.5 cm. polyp 5 cm. above anus	Regional lymph nodes, periduodenal node	Rectal bleeding, acute large intestinal obstruction	Combined resection; well for 32 months; died of peritonitis

serosa, and (2) a type of tumor exhibiting from the very beginning a highly malignant tendency. There is no evidence for this conclusion; benign and malignant rectal carcinoids are histologically identical. The variant clinical behavior of these tumors might be explained on another basis. Most benign rectal carcinoids are situated beneath an intact mucosa; as a consequence, symptoms appear late or not at all. This could provide the opportunity for malignancy to develop before the existence of the tumor is suspected. Raven studied rectal carcinoids and concluded that "the formation of metastases is only a matter of time, although the degree of malignancy is were small, benign and asymptomatic. Three of these tumors were found incidentally at autopsy and do not merit further description. The fourth benign tumor was discovered by physical examination and proctoscopy; this case is described briefly after the presentation of the case with metastases.

Case 35.—A 34-year-old Negro female was admitted January 16, 1944, because of acute large intestinal obstruction of 16 days' duration. There was a long but indefinite past history of constipation, frequent eructation, and "indigestion" not related to meals. For several weeks prior to admission she had occasionally noted bright red blood on stools after straining; this she attributed to her known hemorrhoids. Despite the use of enemas and cathartics she had had no bowel

movement during the 16 days preceding admission, but had been able to pass flatus occasionally. Vomiting and abdominal cramps developed and became progressively worse, causing the patient to seek medical attention.

On admission she appeared malnourished, moderately dehydrated and chronically ill. The abdomen was moderately distended and nontender. The right side of the large intestine was filled with hard feces. On rectal examination a firm, pedunculated, freely-movable polyp 2 cm. in diameter was felt on the right posterolateral wall about 2 inches from the anus. The hemoglobin was 54 per cent of normal.

Roentgenograms after a barium enema were unsatisfactory because of retained feces despite vigorous efforts to clear the intestine with enemas. After one enema there was a sudden passage of about 500 cc. of bright red blood. Sigmoidoscopy was done the same day and the previously noted polyp was biopsied. The mucosa overlying the polyp contained a small ulcer and this was presumed to be the source of the bleeding as no other abnormalities were found. On microscopic examination the biopsy showed nests of atypical epithelial cells in the submucosa; some of the cells tended to form acini. Definite pleomorphism and numerous abnormal mitoses were seen. The diagnosis of the biopsy was benign rectal polyp with partially differentiated adenocarcinoma in the base.

Despite adequate conservative therapy, the patient's abdominal distention increased. Inasmuch as the rectal polyp was obviously not obstructive, a second lesion higher in the left colon was assumed. A cecostomy was done 5 days after admission, following which the patient improved.

No organic obstruction of the colon was found at exploratory laparotomy on February 8, 1944; the ileus was presumed due to kinking of the redundant rectosigmoid. The liver and other structures were not remarkable. A nodular tumor mass about 8 cm. in diameter was felt beneath the peritoneal reflection posterior to the rectum, between the rectal wall and the sacrum. This mass was adjacent to the polyp palpable within the rectal lumen. A combined abdominoperineal resection of the rectum was done.

The surgical specimen (Fig. 1) measured 22 cm. in length. Attached to the external surface of the middle third were 4 conglomerate, irregularly ovoid masses, the largest of which measured 6.5 cm. in greatest dimension. These masses varied from soft to moderately firm in consistency and were encapsulated by a thin brownish-red membrane continuous with the serosa of the rectum. The cut surfaces of the masses bulged and varied in color from red to reddish-brown. The normal rugal pattern of the rectal mucosa was absent in the middle third. In this portion of the specimen, 5 cm. proximal to the pectinate line, was a firm polypoid tumor 1.5 cm. in diameter attached by a pedicle 0.8 cm. in diameter. The mucosa over the tumor was grossly intact. On cut section the tumor did not appear to extend into the muscular layer of the rectal wall. Microscopically, the rectal tumor consisted of masses of typical carcinoid cells situated in all layers of the intestine; a few of the cells were arranged into well-formed glands. Atypical forms and abnormal mitoses were moderate in number. Numerous lymphatic vessels contained tumor cells in their lumens. An argentaffin stain of the tumor was positive. The masses adjacent to the rectum, one of which was identified as a lymph node, contained identical tumor tissue. The pathologic diagnosis was malignant carcinoid of the rectum with metastases to regional lymph nodes.

The patient's immediate postoperative course was complicated by a wound abscess; however, she was discharged in good condition on March 28, 1944. The cecostomy had closed spontaneously, the permanent colostomy was functioning well, the patient was gaining weight, and her anemia had improved.

The patient was well for 32 months after discharge; during this period she had no complaints and gained 48 pounds. On November 18, 1946, the colostomy suddenly ceased to function. The patient was re-admitted 3 days later with typical findings of acute intestinal obstruction. Beneath the old midline incision was a nodular, tender suprapubic mass measuring 4 in. in diameter to which the colon was adherent just proximal to the colostomy. The patient ran a progressive septic fever. Seven days after admission the abdominal mass had become fluctuant and was incised and drained of 200 cc. of foul green pus. The abscess cavity appeared to extend into the peritoneal cavity. Postoperatively, the patient's blood pressure fell to shock levels and did not respond to vigorous therapy; she died 2 days later.

At autopsy there was diffuse peritonitis, presumably secondary to the extensive subcutaneous abscess. *Proteus vulgaris* was cultured from the heart's blood, the abscess cavity and the peritoneal exudate. There was no recurrence of tumor in the pelvis or in the colostomy. The liver was not remarkable. A solitary, gray, ovoid mass measuring 1.0 by 2.0 cm. was found near the duodenum in the hepato-duodenal ligament; this tumor was composed of carcinoid cells on microscopic examination, but an argentaffin stain was negative.

Comment. It is interesting to note that in this case combined resection of the rectum was performed under the erroneous impression that the tumor was an adenocarcinoma. However, this treatment was unquestionably correct, as demonstrated by the patient's survival for 32 months—the longest survival reported in a case of malignant rectal carcinoid. Three cases have been reported in which biopsies from benign rectal carcinoids were mistakenly diagnosed as carcinoma, leading to perhaps unnecessary resection of the rectum.[61, 75] In the following case it will be seen that a similar operation resulted from an erroneous interpretation of the gross findings despite a correct biopsy diagnosis.

Case 38.—A 56-year-old Negro female was admitted to the Gynecology Service on July 7, 1951, because of intermittent post-menopausal vaginal bleeding of one year's duration. Two months before admission she had a 3-week attack of "intestinal flu" characterized by fever and lower abdominal pain but not by change in bowel habits. During and since this illness she had lost 11 pounds.

The patient appeared malnourished on admission. Pertinent physical findings were confined to the pelvis and rectum. The cervix was normal. The uterus was small, markedly retrodisplaced, and tightly adherent posteriorly. The adnexae were not remarkable. A hard irregular, immovable mass measuring 2.0 cm. in diameter protruded into the rectal lumen from the left lateral wall about 8 cm. from the pectinate line. This mass appeared to be attached to the fundus of the uterus.

The specimen obtained from a uterine curettage was not remarkable. Fluoroscopy and roentgen rays following a barium enema showed a deviation of the rectosigmoid junction which suggested the presence of extrinsic pressure or an intrinsic filling defect, but no definite diagnosis could be made. The rectal mass was examined and biopsied through a sigmoidoscope. The mucosa overlying the mass appeared to be intact, but was edematous and bled easily. At this examination it was again noted that the retrodisplaced uterus was adherent to the rectal mass, and that both were attached to the left posterolateral wall of the pelvis. In the rectal biopsy there was a microscopic focus of carcinoid cells in the submucosa, with no evidence of local invasion or metastasis.

The patient was transferred to the surgical service and an exploratory laparotomy was done on August 22, 1951. The fundus of the uterus was firmly adherent to a 4 by 6 cm. mass in the left adnexal area which appeared to be an old healed pyosalpinx. This mass and the entire uterus were resected. The rectal mass, which occupied the space beneath the peritoneal reflection just inferior to the left adnexal mass, was thought to be an operable malignant tumor. A combined abdominoperineal resection of the rectum was done.

Examination of the surgical specimen revealed extensive chronic suppurative inflammation of the uterine tube, rectum and pelvic soft tissue. The hard, fixed, infiltrating rectal mass was composed of inflammatory tissue. The microscopic focus of carcinoid cells was again identified in the submucosa; there was no evidence of malignancy.

Comment. This case raises the question of the proper treatment for rectal carcinoids. The ultimate answer must be based upon knowledge which we do not possess at this time. Nine (12 per cent) of 74 reported cases of rectal carcinoid are known to have been actually malignant; how many of the remainder were potentially malignant is unknown. Some authors believe that all rectal carcinoids are actually or potentially malignant. The present evidence seems to indicate that, even if there are no genuinely benign rectal carcinoids, most of these tumors reveal their malignant character very slowly.

Local excision of the tumor has been practiced and recommended by several authors.[8, 19, 20, 30, 68] This was the only method of treatment of 30 benign tumors, of which 24 were followed for two months to nine years with no recurrence or appearance of metastases.

In a recent report Shepard, Strug and DiLeo[61] considered the problem of treatment at length and concluded that single nodules 1 cm. or less in diameter might be locally excised, with careful microscopic study of the specimen to be sure of complete removal. This should be followed by combined resection of the rectum if the

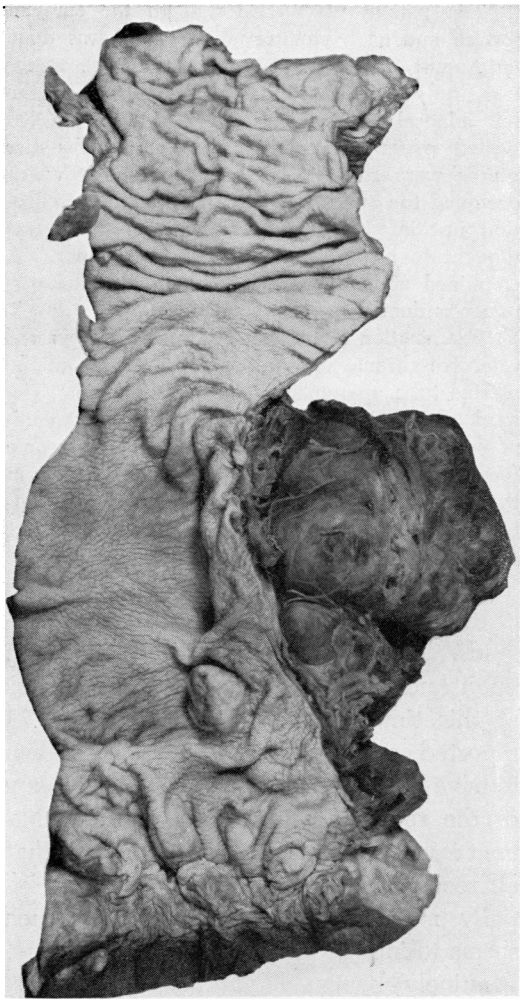

FIG. 1.—Surgical specimen, Case 35, malignant carcinoid of the rectum. The primary tumor is a 1.5 cm. polypoid tumor situated 5 cm. from the pectinate line. Several large metastases are seen in the peri-rectal tissues; these masses were situated posteriorly, between the rectum and the sacrum.

microscopic examination revealed tumor beyond the line of excision or if tumor cells had invaded to the serosa. They recommended combined resection of the rectum for all tumors over 1 cm. in diameter, all ulcerated or infiltrating tumors, and all tumors having multiple sites of origin.

In determining the proper course of treatment, the size of the tumor is obviously an important factor; in general, the larger the tumor, the more likely it is malignant. However, there is no arbitrary size, such as 1 cm., beyond which a tumor can be assumed to be malignant on this basis alone. In one case reported by Stout the tumor measured 2.0 cm. in diameter; the patient was alive and well nine years after local excision. The presence of multiple tumors does not in itself indicate malignancy, since two of three such cases were benign.[27] Invasion of other layers of the rectal wall by tumor cells arising in the submucosa, as shown on microscopic examination, is not a good criterion of malignancy, since it has been seen repeatedly in so-called benign tumors which were successfully treated by local excision.

On the basis of present knowledge, the following courses of treatment are suggested. It is assumed that an adequate preoperative biopsy has been taken in every case.

1. Local incision is proper for small tumors in cases where there is no evidence of malignancy, such as fixation of the tumor, enlarged liver, intestinal obstruction or symptoms of hepatic insufficiency. A generous margin of grossly normal tissue should be excised with the tumor, and the specimen should be carefully examined to be sure of complete removal. Ulcerated tumors should be studied with special care. If this examination reveals infiltration of tumor cells through the serosa into the peri-rectal tissues, or infiltration along the submucosa beyond the margins of the specimen, or tumor emboli in lymphatic vessels, the entire rectum should be resected subsequently. In cases where local excision has been the only method of treatment, the patient probably ought to be reexamined regularly for evidence of recurrence, although no instance of recurrence at the primary site has ever been reported.

2. Combined abdominoperineal resection of the rectum is the treatment of choice in the following categories:

a. Large tumors. Two centimeters is tentatively suggested as the critical diameter. This would include all tumors which cannot be locally excised with an adequate margin of normal tissue without compromising the rectum.

b. Annular constricting lesions.

c. Tumors fixed to the peri-rectal tissues.

d. Recurrent tumors.

e. All obviously malignant tumors, except those in group 3 (below).

3. The courses of most patients with malignant rectal carcinoids have been rapidly fatal. In view of this, palliation alone would seem to be indicated for cases with widespread metastases, as demonstrated by enlarged liver or symptoms of hepatic insufficiency. In contrast to the experience with small intestinal carcinoids, widespread metastasis from a rectal carcinoid is not compatible with long existence.

ASSOCIATED MALIGNANT TUMORS

In the series of carcinoid tumors reported in 1949 by Pearson and Fitzgerald,[52] nine (31 per cent) of 29 tumors found at autopsy were associated with a malignant tumor of a different histologic type. They believe that all carcinoid tumors are malignant and, therefore, that these are cases of double primary malignancy. Their finding is contrasted sharply with the incidence of double primary malignant tumors of all types, which has varied from 0.3 to 8 per cent in many series.[65, 66] In another recent series, Warren and Coyle[70] found that ten (53 per cent) of 19 asymptomatic carcinoids were associated with other malignant tumors.

In the series reported here, seven (47 per cent) of 15 carcinoid tumors found at autopsy were associated with a malignant tumor of a different type (Table I). Six of the carcinoid tumors were situated in the ileum and one of these had metastasized; the seventh carcinoid was in the appendix. Five of the associated tumors were carcinomas and were primary in the breast, lung, liver, pancreas and adrenal. The primary sites of the other two associated tumors were not determined; one was a lymphosarcoma and the other a plasma cell myeloma. In addition to these cases, one carcinoid was found in an appendix removed incidental to a hysterectomy for carcinoma of the cervix.

Disregarding the question of statistical significance, these findings cannot justify the concept of a higher incidence of double malignancy unless it is assumed that all carcinoid tumors, "benign" and "malignant," are actually malignant. This assumption is without proof at the present time, but every recent author has concluded that it is probably correct. This author is inclined to agree, believing that all carcinoid tumors are potentially malignant and that all will become manifestly malignant if permitted to fulfill their natural course.

SUMMARY

1. Thirty-eight carcinoid tumors were reported; 19 of these were in the appendix, 14 were in the small intestine and five were in the rectum.

2. Seventeen of the 38 tumors were invasive in the sense that tumor cells were found in layers of the intestinal wall other than the submucosa.

3. Four of the small intestinal tumors and one of the rectal tumors were malignant, as indicated by metastases to the regional lymph nodes or farther.

4. All previously reported cases of malignant carcinoid of the rectum were summarized in Table V. These data indicate that malignant carcinoids of the rectum are more rapidly fatal than malignant tumors of the small intestine.

5. Criteria were suggested for the treatment of rectal carcinoids.

6. It was concluded that all carcinoids are potentially malignant.

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