Carcinoid Tumors of the Gastro-Intestinal Tract

(The so-called Argentaffine Tumors)

Theodore S. Raiford, M.D.

(From the Departments of Surgery and Surgical Pathology, Johns Hopkins Hospital and University)

There is perhaps no group of tumors which has been so widely discussed during recent years as the "carcinoids," or "argentaffine tumors." While by no means constituting a new pathological entity, they present interesting problems of clinical and pathological significance.

It is difficult to contribute at this time to the histogenesis of the carcinoids. Masson and others have demonstrated through intensive studies the origin of these tumors from the so-called chromo-argentaffine or Kultschitzky cells of the intestinal mucosa. It is the purpose of this paper to summarize the present knowledge and report a group of cases observed in this laboratory, discussing their clinical and pathological significance.

In a review of the material in the pathological laboratories of the Johns Hopkins Hospital, 29 carcinoid tumors were found. This number occurred among some 62,000 specimens of all kinds, including autopsy material and specimens removed at operation; 1,611 of these were tumors of the gastro-intestinal tract, placing the incidence of the carcinoids at 0.18 per cent.

Historical

Forbus has presented an excellent and detailed historical review of the carcinoid tumors and for those who are interested in
that phase of the subject his article, published in 1925, is recommended. He reported in addition 6 cases of carcinoids of the appendix. None of his cases had metastasized, and he, like Oberndorfer, called attention to their harmless character. A number of metastasizing carcinoids have been reported during recent years. Cooke, summarizing all reported cases occurring in the small intestine, found metastases in 26 per cent. Of his own 11 cases, 27 per cent were malignant. He emphasized the fact that, although benign in appearance, the carcinoids frequently metastasize, similar to carcinomas elsewhere in the gastro-intestinal tract. Marangos believes that in time all carcinoids become malignant, due to invasion of the blood vessels by tumor cells, and that the malignancy of the tumor varies with its size. Gáspár agrees, but believes that the tumors may metastasize through the lymphatic system as well.

Masson's work on the histogenesis of carcinoids is a valuable contribution and will be considered more fully in a later section.

**Location**

The 29 carcinoids observed in this laboratory were distributed throughout the gastro-intestinal tract as follows:

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>9</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1</td>
</tr>
<tr>
<td>Jejunum</td>
<td>1</td>
</tr>
<tr>
<td>Ileum</td>
<td>7</td>
</tr>
<tr>
<td>Appendix</td>
<td>17</td>
</tr>
<tr>
<td>Tip</td>
<td>12</td>
</tr>
<tr>
<td>Middle</td>
<td>3</td>
</tr>
<tr>
<td>Base</td>
<td>2</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>2</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
</tr>
<tr>
<td>Rectum</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>

The appendix is by far the most common location of carcinoid tumors. The small intestine is the seat of the lesion in approximately half as many cases, whereas the tumors are of extreme rarity elsewhere in the intestinal tract. Seven of the tumors of this series in the small intestine were located in the terminal ileum and one of those in the colon was in the cecum. The region of the ileocecal valve, therefore, was the site of roughly 85 per cent of the tumors.

It is difficult to explain the frequency of carcinoids in the appendix, especially since that organ is so rarely the seat of neoplastic growth. A factor of great clinical importance is that
the carcinoids of the appendix usually produce obliteration of the lumen, with consequent symptoms of chronic appendicitis, thereby attracting the early attention of the clinician. It is quite probable that identical tumors in the remainder of the intestinal tract, causing no symptoms, frequently escape discovery. The distribution of the chromaffin cells in the intestine may be relevant to the distribution of the tumors, in that these cells are more common in the sites where the tumors are most frequent. This will be discussed more fully under histogenesis.

**Fig. 1. Chart Showing the Ages of Greatest Incidence of Carcinoid Tumors**

The various locations are indicated by different lines. The appendix curve reaches its peak in the second decade. In sharp contrast to this the curves of the remaining portions of the tract lie entirely between the fifth and seventh decades.

**Age, Race, and Sex**

Carcinoids are not peculiar to any age group. The oldest patient in this group was sixty-six years of age and the youngest twelve. The average age was thirty-five. In analyzing the cases according to their location, a most interesting observation was made. The appendiceal tumors occurred at an average age of twenty-five years, while the average ages for carcinoids in the small intestine and the colon were fifty-five and forty-five years respectively. This is illustrated graphically in Figure 1. The appendix curve reaches its peak in the second decade, thereafter
dropping to zero, while the curves for the small intestine, colon, and stomach reach their peaks in the fifth decade or after. This can be explained on the basis of early recognition of symptoms in the appendix, as stated above. It would seem, therefore, that carcinoid tumors occur commonly in youth, but are seldom recognized unless so located as to cause acute symptoms. There is nothing significant in the race or sex distribution.

**Clinical Features**

There is little to be said in regard to the distinguishing clinical features of carcinoid tumors. Brief reports of the cases of this series with their outstanding clinical findings are appended.

*Stomach and Large Intestine:* In the stomach, colon, and rectum the carcinoids produce the symptoms of any gastro-intestinal tumor. All of the tumors in these organs were malignant. They did not, however, produce the marked general symptoms of malignancy—cachexia, anemia, and loss of weight. Diarrhea is of common occurrence, but melena is rare. The presence of these features in one case led a house officer to suggest the diagnosis before operation. This cannot, however, be regarded as a reliable means of diagnosis. No doubt there are many tumors which escape observation. The rate of growth of a carcinoid tumor is extremely slow, and since no symptom is apparent before partial obstruction, a considerable time elapses before the condition is recognized.

*Small Intestine:* The majority of tumors in the small intestine are apparently benign, causing no symptoms unless of sufficient size to produce obstruction. Two of our nine cases were malignant and had metastasized to the lymph nodes and the liver. In
such a case obstruction may be recognized early if the lumen of the small bowel is occluded. All of the benign tumors, however, were asymptomatic and were discovered only at autopsy.

**Fig. 3 (Path. No. 47648, Case 11). Drawing of a Carcinoid of the Appendix, Actual Size**

The gross specimen depicted shows a large, bulbous appendix over which the vessels are tortuous and enlarged. There is a small amount of peritoneal fat attached to the specimen. The drawing on the right illustrates sections taken at various levels through the tumor. The tumor consists of a dense growth surrounding the lumen, which is almost entirely occluded. In the two larger sections the fibrous capsule can be plainly seen. (Case of Dr. T. S. Cullen)

**Fig. 4 (Path. No. 47648, Case 11). Photograph of Serial Blocks Through the Tumor Shown in Fig. 3**

The sections from left to right represent their order in the tumor from base to tip. The tumor is seen to occlude the lumen and is surrounded by a dense fibrous capsule. (Case of Dr. T. S. Cullen)

**Appendix:** A different situation exists in the appendix. The symptoms are usually those of chronic appendicitis, brought on by obliteration of the appendiceal lumen. This, of course, occurs only when the tumor is of sufficient size; otherwise no symptoms are produced. In a few cases the tumor of the appendix has been so large as to be palpable on physical examination.
Although considerable work has been done in attempting to establish the relationship of the carcinoids to the endocrine system, no one has recognized any definite resulting metabolic change. Hence a preoperative diagnosis of the specific type is impossible.

**Pathology**

*Gross Pathology:* The typical carcinoid tumor is usually recognized as a small nodule in the submucosa of the bowel. It is firm, rubbery, and moves freely beneath the mucous membrane. It may assume a pedunculated form, as in Figure 2. The cut surface has a bright yellow color. In the appendix the mucosa is usually lifted until it is in approximation with the opposing wall. The appendiceal carcinoids are most frequently located at the tip of the organ, more rarely in the base and the mid-portion (Figs. 3 and 4). The size varies, but they are usually between 5 and 10 mm. in diameter. Larger tumors have been observed, but are rare. The more malignant tumors are not limited in size. They may be as large as any of the more common malignant neoplasms. In one case of the series the ascending colon was completely surrounded and constricted by a tumor which was mistaken for the so-called "napkin-ring" carcinoma (Fig. 5).

Multiplicity has been regarded by some writers as characteristic. While occurring not infrequently, it cannot be regarded as typical. In only two of this series of 29 cases were multiple tumors found.
The cells occur in discrete nests, separated by a dense stroma of connective tissue. The nuclei are small and uniform. The cytoplasm is profuse, but has no distinct cell border.

The tumor is arranged in discrete nests separated by a moderate amount of connective-tissue stroma. The nuclei are fairly large and heavily dotted with chromatin particles. They are uniform in size. The cytoplasm is granular, but no cell outline can be seen. (Case of Dr. T. S. Cullen)
Metastases, if present, are first found in the regional lymph nodes. Distant metastases show a surprising preference for the liver, where, as in the glandular metastases, the bright yellow color is preserved.

Frequently the tumor may be large and feel firm and hard, but upon section, much of it is found to consist of a dense, white, fibrous capsule which surrounds the softer, yellow tumor. This is essentially a fibrous reaction which consistently accompanies the tumor growth.

Simon has classified the tumors according to their location as mucosal, submucosal, and muscular. Such grouping hardly seems necessary, since all of the tumors arise in the submucosa and later grow into the muscularis, the progress and growth being governed by the age of the tumor and the part of bowel in which it arises. Ulceration of the mucosa with subsequent hemorrhage is rare.

**Microscopic Picture:** A partial similarity between the carcinoids and true carcinomas has no doubt been responsible for the confusion existing as to the relation of the two tumors and the inability of older pathologists to distinguish one from the other. Nevertheless, the minor differences in structure must have been apparent to lead Lubarsch to designate them "primary carcinomata" and Oberndorfer to give them the name "carcinoids."

The morphology of the carcinoids is strikingly uniform, whether they be benign or malignant, and regardless of their location (see Figs. 8 and 9). They are supposedly composed of cells arising from the epithelium of the mucosa, growing into the submucosa in nests and columns of varying sizes. The nests of cells may be closely packed together, but are more frequently separated by a dense stroma of connective tissue (Fig. 6). The smooth muscle of the wall commonly undergoes a moderate hypertrophy and together with the connective tissue is responsible for the apparent encapsulation of the tumor cells. This in effect is a false capsule, for after first being formed about the tumor, it is frequently infiltrated by the cells and apparently offers little resistance to their subsequent invasion. The cells form homogeneous masses in which the nuclei are distinct but the cytoplasmic membranes are obscure (Fig. 7). This is almost invariably true with the larger tumor deposits. Smaller cell groups, however, are not infrequently arranged in typical rosettes, resembling strikingly rosettes of neuroblastomas, such as those in nephrogenic tumors. The cells are columnar in shape and have a more distinct cell border. They are vaguely like alveoli of epithelial cells and are no doubt responsible for many diagnoses of adenocarcinoma. Instead of a typical lumen, however, they frequently contain a small droplet of colloid-like material. They are spherical in shape
FIG. 8 (PATH. NO. 47648, CASE 11). OIL-IMMERSION PHOTOGRAPH OF CELLS OF A CARCINOID OF THE APPENDIX (SAME CASE AS FIG. 7)

In this photograph the character of the cells can be seen more plainly. The nuclei vary somewhat in size, but all are more or less round. No definite mitotic figures can be seen, but chromatin particles are abundant. The cytoplasm is quite granular and under this magnification the cell membrane is more distinct. This tumor had not metastasized.

FIG. 9 (PATH. NO. 48429, CASE 23). OIL-IMMERSION PHOTOMICROGRAPH OF A METASTATIC NODULE FROM THE CARCINOID OF THE ASCENDING COLON SHOWN IN FIG. 5

The cells are almost identical with those of the preceding photograph in nuclear shape and size and in cytoplasmic granulation. The essential difference is the lack of cell definition. (Case of Dr. Dean Lewis)
and a longitudinal section of a crypt is practically never seen. In addition to these differences, the cells differ in the granulation of the cytoplasm and their nuclear form. These differences are partially brought out in Figure 10, where tumor cells are shown in contrast with normal epithelial crypts.

Most commonly found in the submucosa, the tumor may invade the muscularis freely. Masson calls attention to its preference for the axial connective tissue in the appendix and the interstitial connective tissue supporting the nerves of Auerbach's plexus in

![Image](image_url)

**FIG. 10 (Path. No. 48429, Case 28). High-power Photomicrograph of the Tumor Shown in Fig. 9**

This area shows a rosette arrangement of the cells similar to that seen in neuroblastomas. The nuclei are of the same type seen in the preceding photograph. Note the absence of a lumen and the heavy granulation of the cytoplasm as compared with the cells of the normal crypts in the lower part of the picture. Under the microscope the cytoplasm of the tumor cells was slightly yellow in color, due to its affinity for the chromates of Zenker's fixative. This is a characteristic of chromaffin tissue.

the intestine. According to this author, the cells may be grouped into three morphological types.

The *round* or *polygonal* cells are most common. They form columns of varying size. The nuclei are regular in size, small, and round, and contain numerous minute particles of chromatin. The cytoplasm is abundant and contains acidophilic granules in varying degrees. Some of the cells contain tiny vacuoles filled with a doubly refracting lipoidal substance. The cytoplasm is bounded by a delicate membrane, which is at times imperceptible.

The *palisade* cells are less common. They are larger, are oblong in shape with the long axis perpendicular to the basement membrane, and form the outer layer of the cell groups. The
Fig. 11 (Path. No. 10023, Case 5). Medium-power photomicrograph of the tumor shown in Fig. 2

Notice the striking similarity of the cells to those of the normal adrenal cortex. The cytoplasm is abundant and well defined, containing a moderate number of granules. The nuclei are small, uniform, and dark staining.

Fig. 12 (Path. No. 10023, Case 5). Oil-immersion photomicrograph of the tumor shown in Fig. 11

This accentuates the similarity between the cells of the tumor and the cells of the normal adrenal cortex. The nuclei are more dense than in the usual carcinoid.
cytoplasm is of the same character and the bases of the cells contain many acidophilic granules. The nuclei are not unlike those of the round cells and are arranged at some distance from the base of the cells. Masson has compared these cells morphologically to those of the adrenal cortex.

The columnar cells are those forming the tiny rosettes referred to above, which resemble cross-sections of a normal crypt. They are similar to the other types of cell except in shape, and no doubt their origin is the same.

It is not to be understood that these three types of cells are at all times clearly defined. Intermediate forms are common, and it is frequently difficult to distinguish one from the other.

Some of the tumors are composed of cells strikingly like those of the normal adrenal cortex. The nuclei are small and stain homogeneously dark. The cytoplasm is moderate in amount, is granular, and possesses a fairly distinct outline. The same connective-tissue stroma is found here as in other tumors of the series. Such a tumor is depicted in Figures 11 and 12.

The stroma of the carcinoids is peculiarly typical. It is a dense tissue varying in amount with different locations, but always present to some degree. It is most dense in the appendix, less abundant in the intestines. According to Masson, it is composed of hypertrophied smooth muscle. Unquestionably there is
a moderate amount of smooth muscle hypertrophy as a reaction to the tumor, but the stroma is made up largely of connective tissue, as can be shown by differential stains such as Mallory's and Van Gieson's. It is connective tissue of a dense, proliferative type, not at all like the loose tissue of the normal submucosa. In places it appears to be hyalinized and seemingly retards the growth of the tumor cells, as in Figure 13.

**Fig. 14 (Path. No. 48429, Case 28). Low-power photomicrograph of a metastatic nodule from the tumor shown in Fig. 5**

This shows the periphery of the nodule containing typical masses of tumor cells included in a dense stroma and surrounded by a heavy fibrous capsule. The nodule has the general arrangement of a lymph node but no lymphoid tissue could be found.

Certain of the metastatic nodules from carcinoids are unlike those from any other malignant tumor. In two of the cases here reported, nodules were found in the mesentery which were supposedly glands containing tumor metastases. On section, however, one was seen to consist of malignant carcinoid cells imbedded in the dense stroma previously described and surrounded by a thick fibrous capsule (Fig. 14). No trace of lymphoid tissue could be found to prove the previous existence of a lymph gland. The nodule from the second case was similar except that at one point were found what appeared to be lymphoid follicles undergoing
regressive change, while in other places accumulations of lymphocytes were seen (Fig. 15). These peculiar nodules are undoubtedly a part of a metastatic process and must be explained on the basis of a local deposit of cells by the blood stream or a lymphatic metastasis in a mesenteric gland. The evidence at hand indicates the latter process, which has stimulated a profuse fibrosis causing complete destruction and replacement of the normal lymphoid structure.

**Histogenesis**

Since the theory accepted at present ascribes the origin of the carcinoid tumors to the so-called chromaffin cells of the intestine, a description of these cells is appropriate.

These peculiar cells were first described by Nicolas Kultschitzky in 1897, as specialized epithelial cells having a characteristic

---

**Fig. 15 (Path. No. 10562, Case 29). Low-power Photomicrograph of a Metastatic Nodule from the Mesentery**

This shows an arrangement similar to the previous case, but there remains a portion of two lymph follicles undergoing regressive change. In another part of the picture there is a small accumulation of lymphocytes. This is without doubt a metastasis to a lymph gland which has entirely replaced the normal structure, with the characteristic fibrosis noticed in the previous case.
Carcinoid Tumors of Gastrointestinal Tract

structure. Schmidt restudied them in 1905 and, noting their yellow color, called them "gelben Zellen." He concluded that they were a part of the chromaffin system and similar to the cells of the adrenal medulla. Gosset and Masson found in 1914 that certain granules in the cytoplasm had the power of reducing silver compounds, leaving brown or black particles. In view of this affinity for silver they called the cells "argentaffine." By subsequent investigators they have been called "entero-chromaffin cells" (Ciaccio) and "chromo-argentaffine cells" (Cordier).

The cells are found in all parts of the intestinal tract of man and many of the higher vertebrates. They differ in number with the location, being most numerous in the appendix and terminal ileum, where from five to ten may be found in each crypt. They are less common in the colon and upper small intestine and comparatively rare in the stomach and rectum. They are concentrated at the bases of the crypts, where they are pear-shaped, with broad bases lying on the basement membrane and narrow bottle-shaped necks leading up to the lumen of the crypt. The cytoplasm stains lighter than that of other epithelial cells, but scattered throughout are numerous acidophilic granules. The nucleus is round, uniform in size, and located near the center of the cell. It contains a finely reticulated network with numerous small chromatin particles. Stained by the silver impregnation technic of Gosset and Masson, the cytoplasmic granules appear as tiny brown or black particles.

The origin of the cells is still a mooted question. Masson, on the basis of their appearance in regenerating epithelium and their occasional occurrence in malignant tumors arising from the epithelial cells, attempts to explain them as differentiated epithelial cells of entodermal origin. Kull, studying them in the chicken embryo, concluded that they were of mesenchymal origin. It would seem to the writer that they are cells of ectodermal origin which have migrated early in life from the neural crest and become adapted to a special function in forming a part of the general chromaffin system. In favor of this mode of origin is the striking similarity of the cells of certain tumors to the cells of the adrenal gland, not only in morphological form but also in the gross color of the tumor. The affinity for silver exhibited by the tumor cells is not present in epithelial cells, but is possessed by many cells of ectodermal origin. As has already been pointed out, the appearance of rosettes in typical carcinoids links them to the neuroblastomas.

The function of the cells is likewise unknown. Masson regards them as forming a diffuse endocrine organ and, through secretion of a substance which he designates as "neurocrine," exerting a
regulatory influence upon the proliferation of the smooth muscle fibers of the intestinal wall, especially those of the muscularis mucosa. By this he explains the smooth muscle hypertrophy coincident to the carcinoid tumors, especially those located in the appendix. This hypothesis cannot be accepted without reservation. First, the uniform presence of an extreme smooth muscle hypertrophy must be questioned. Differential stains on sections of selected cases in this series indicated an excess of fibrous connective tissue and only moderate if any muscular hypertrophy. Second, the presence of such a substance as neurocrine has never been proved and, if it were, the demonstration of any regulatory effect upon the muscular components of the intestine would be extremely difficult.

Ciaccio contends that the cells are similar in function to those of the adrenal medulla and secrete adrenalin directly into the intestinal tract. While this theory is plausible, it has not been proved by conclusive experimental work.

There remains the correlation of these normal argentaffine cells with the carcinoid tumors. That the tumors arise from these cells is generally conceded. The similarity in both staining reaction and microchemical properties gives striking evidence of their relation. It is also occasionally possible to observe the growth of a tumor directly from the cells in the crypts.

Masson contends that the normal cells migrate first to nerves of the submucous plexus, where they may normally be found within the substance of the nerve. In this location, proliferation forms neuromata, and these in turn are directly responsible for subsequent tumor formation. Perhaps this is true. One occasionally does find a neurogenic hypertrophy coincident with carcinoid formation, and it is true there are cells in proximity to the nerves which strikingly resemble tumor cells. They are possessed, however, of a perineural and not an intraneural arrangement, and I am not convinced that they signify more than a secondary invasion of the nerve sheath. In the 29 cases of this series, including tumors from all parts of the intestinal tract, neurogenic hypertrophy was in evidence in only a few cases located in the appendix. Therefore, while there is excellent reason to believe that the tumors arise from the normal argentaffine cells, the presence of argentaffine neuromata as intermediary stages must be questioned.

To summarize, it is ascertained beyond reasonable doubt that the carcinoid tumors arise from the cells of Kulitschitzky or the chromo-argentaffine cells of Masson, and that these cells are normally present in the intestinal tract of man. They are thought to be chromaffin in nature, and the tumors are consequently chromaffin tumors. Their significance, or the stimulus resulting in tumor formation, can at best remain a matter of speculation.
MALIGNANCY

Although carcinoids are commonly regarded as benign tumors, it must be recalled that in two of the earliest cases reported, namely those of Ransom and Notthafft, metastases were noted. During subsequent years, however, there existed doubt as to whether these were true carcinoids or atypical carcinomas, and, until the last few years, the majority of writers have regarded the tumors as relatively benign. In reviewing the histories of the cases in the series upon which this paper is based, it was found that one of the metastasizing carcinoids was originally diagnosed appendiceal carcinoma. Within the past five years several cases have been reported from various clinics which were definitely malignant and in which the diagnosis has been confirmed by the silver stain.

Of the cases of this series 20.7 per cent were malignant in nature, having metastasized to regional glands or beyond. It is of interest to note that while the incidence of carcinoid tumors is greatest in the appendix, the malignant tumors are relatively infrequent in that location, while all the tumors occurring in the stomach and large bowel had metastasized. This is shown graphically in the accompanying table.

**Table I: Incidence of Malignancy in Carcinoids**

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Number</th>
<th>Malignant</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1</td>
<td>1</td>
<td>100.0</td>
</tr>
<tr>
<td>Small intestine</td>
<td>9</td>
<td>2</td>
<td>22.0</td>
</tr>
<tr>
<td>Appendix</td>
<td>17</td>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>Large bowel</td>
<td>2</td>
<td>2</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The occurrence of metastases from tumors which are commonly regarded as benign would seem to be of sufficient importance to justify detailed description. Hence the malignant carcinoids of this series will be reported at some length.

**Case 1 (Path. No. 40700): Clinical Features:** It is unfortunate that few data were obtainable on this case. In a brief note that accompanied the specimen to the laboratory it was stated that the patient was a white male, fifty-five years of age, who had suffered from vague attacks of indigestion for ten months and during that time had lost 15 pounds weight. Carcinoma of the stomach had been suspected and an exploratory laparotomy performed, revealing an inoperable growth of the stomach with metastases to the liver and lymph nodes. Nothing was done at the operation, and the patient died a few days later, coming to autopsy.

**Gross Pathology:** A mass which appeared grossly to be carcinoma was found in the greater curvature of the stomach. Metastases had occurred in the adjacent lymph nodes and liver, as evidenced by large hard glands and a large solitary nodule in the liver.

**Microscopic Pathology:** The material received in this laboratory consisted of microscopic sections from the primary tumor in the stomach, from the involved
lymph nodes, and the liver nodule. As seen in the section from the original growth the tumor was composed of atypical cuboidal cells growing compactly in nests and strands. These had apparently originated in the submucosa, but had grown in all directions, infiltrating and invading the muscular coats and extending to the subserosal space. These groups of cells were surrounded and supported by a stroma composed of peculiarly dense connective tissue. The individual cells were uniform in size, cuboidal or polygonal in shape, but were separated by no clearly defined cytoplasmic membrane. The cytoplasm was granular, and some of the cells contained tiny vacuoles. The nuclei were small and uniform in size and, although they contained many chromatin particles, few mitotic figures could be seen. In some portions of the tumor the cells simulated the strands formed by adenocarcinomas, but at no place were the alveolar shape and form duplicated. No tissue was available for special stains, but in view of the typical arrangement of the cells the pathologist felt that this was without doubt a tumor of the carcinoid type.

**Diagnosis:** Carcinoid or argentaffine tumor of the stomach with metastases to the regional lymph nodes and liver.

**Result:** Death, following operation.

**Comment:** In view of the rarity of carcinoid tumors elsewhere than in the appendix and small intestine, and the fact that diagnostic stains were not done, the validity of the diagnosis in this case will no doubt be questioned. In answer to the first argument it may be said that the cells of origin, the so-called cells of Kulchitzky, are found in the stomach as well as in the intestinal tract. They are less numerous, it is true, but are present in sufficient numbers to justify the assumption that carcinoids may arise in this location. It has been stated by competent pathologists that for one familiar with the carcinoids, the silver reaction is not essential for a diagnosis. The type of cell and the arrangement are so typical that the nature of the tumor can be recognized at a glance.

This tumor, if it can be considered a true carcinoid, is unique in its occurrence, since few similar cases were found in a thorough review of the literature. Although entirely inadequate, the brief clinical note includes one important feature which is believed to be characteristic of the malignant carcinoids: the paucity of symptoms is greatly out of proportion to the extent of the malignancy as exhibited by the presence of metastases. It is only when these secondary growths are advanced and widespread that constitutional symptoms become marked.

**Case 3 (Path. No. 31805; Case of Dr. C. R. Oden): Clinical Features:** A. M., a white female aged forty-five, entered the hospital complaining of acute abdominal pain. One year before, in 1921, she had undergone an operation in the same hospital for acute cholelithiasis, at which time the gallbladder was removed. Exploring the abdomen the operator found that a portion of the small intestine had formerly been resected. When questioned regarding this, the patient stated that twelve years before she had undergone an operation in another hospital but was unable to recall the name of the operator or what was done at the time. Recovery following the cholecystectomy had been uneventful. Six months later the patient began to have intermittent attacks of vague lower abdominal pain and to suffer loss of appetite, although her general condition remained good. The attacks in-
creased in frequency and severity, the last one having begun three days before admission. It was marked by abdominal distention, vomiting, and pain of a more acute nature. On examination the patient was evidently in acute pain but without showing the effects of a ravaging illness. The abdomen was moderately distended and tender, with muscle spasm over the lower right quadrant. The temperature and leukocyte count were slightly elevated. Immediate operation for relief of acute obstruction was advised.

Operation (1922): On opening the abdomen the operator found the terminal ileum involved in what appeared to be an inflammatory mass. Resection was performed, followed by a lateral entero-enterostomy. Observing the removed specimen after operation, the operator felt that it was a malignant tumor rather than inflammatory in nature. The patient made an uneventful recovery and was discharged from the hospital three weeks after operation.

Ultimate Course: For a while the patient continued to improve, then began to lose weight and suffer from abdominal discomfort and constipation. Having previously confirmed his impression that the tumor was malignant, the first operator felt that this signified a recurrence and refused another operation. An exploratory laparotomy was performed elsewhere and multiple metastases were found. Death occurred shortly afterward from the effects of the tumor.

Gross Pathology: The specimen consisted of a portion of the small intestine which was involved by a neoplastic growth, the size of an egg, practically occluding the lumen of the bowel. Incorporated in the mass were two or three large ovoid nodules which were evidently lymph nodes. When cut the tumor was solid throughout and had the appearance of being quite cellular. The larger mass was apparently primary in the intestinal wall and was covered internally by intact mucosa and externally by edematous serosa. It did not encircle the gut but was of sessile form and had produced obstruction by encroaching upon the lumen.

Microscopic Pathology: The tumor was composed of solid sheets of epidermoid cells growing in a malignant manner and entirely destroying the normal architecture of the bowel. The stroma, scanty in the center of the tumor, was well developed near the advancing borders and was composed of hypertrophied connective tissue. The cytoplasm of the cells was abundant and confluent. The characteristic granulation and vacuolation were present but not marked. The nuclei were large, and numerous mitotic figures were seen. Although no silver stain was done, the morphology was so characteristic as to justify the diagnosis of carcinoid tumor.

Diagnosis: Carcinoid or argentaffine tumor of the ileum with metastases to the regional lymph nodes and later to the peritoneum.

Result: Death; metastases.

Comment: This is one of the few malignant carcinoids whose initial manifestations were those of intestinal obstruction, accounted for, no doubt, by the small size of the affected bowel. Although present at the time, the metastases apparently played little part in the production of symptoms in the early stages of the disease. That the growth was highly malignant was shown by the widespread metastases after the operation in 1922.

It would be extremely interesting to know what was done at the first operation. No doubt some pathological lesion existed at that time to necessitate resection of part of the bowel, but it would be hard to conceive of it as a part of the process which eventually killed the patient, since twelve years had elapsed.
CASE 4 (PATH. NO. G–10048):  

Clinical Features: A white male, aged fifty-seven, entered the hospital with symptoms of nine months' duration referable to a chronic bronchial obstruction. Physical and x-ray examination supported the diagnosis of a bronchial neoplasm, and this was confirmed by bronchoscopy and biopsy. There were no symptoms or physical signs indicative of gastro-intestinal pathology. Three days after admission the patient developed signs of bronchopneumonia, and died two days later.

Gross Pathology: A tumor which had the gross appearance of carcinoma was found obstructing the bronchus leading to the right lower lobe. Metastatic nodules were present in the left kidney, the lower end of the right humerus, and the liver. During routine examination there was found in the lower ileum an ovoid nodule 5 cm. long and 2 cm. wide. This projected into the lumen of the bowel but did not cause any marked degree of obstruction. It was located in the submucosa, and the intact mucous membrane was freely movable above it. When cut through, the tumor was of a fairly firm consistency and was lemon yellow in color. The regional lymph nodes in the mesentery were enlarged and on section some of them showed yellow spots of tumor metastasis. The liver nodule was similar to the intestinal tumor in gross appearance, while the secondary growths in the kidney and bone were white and of a fibrous consistency, as was the primary tumor in the bronchus. It was concluded, therefore, that the liver nodule represented a metastasis from the intestinal tumor.

Microscopic Pathology: The bronchial tumor was a typical squamous-cell carcinoma and the metastases in the humerus and kidney were proved microscopically to be of the same type. The growth in the intestine was of an entirely different nature. It was composed of homogeneous masses of cells arranged in discrete nests and strands. The small hyperchromatic nuclei were uniform in size and did not present a striking picture of mitotic division. The cytoplasm was abundant and granular but poorly demarcated. The cytoplasmic granules were most abundant at the bases of the cells and stood out as dark brown or black dots when stained by the silver impregnation method of Hasegawa. The stroma was abundant and composed of dense strands of connective tissue. The mucosa was not involved, but the tumor cells had invaded the muscular coats and extended through to the subserosa. Sections of the enlarged lymph nodes showed the normal structure largely replaced by tumor tissue similar in type to that of the primary growth, including the same degree of fibrosis. Sections of the liver nodule revealed strands of carcinoid tumor cells invading the normal liver tissue and stimulating a fibrous reaction, resulting in scarring. The cells in these secondary growths contained cytoplasmic granules which showed an affinity for the silver stain, thereby identifying them definitely as metastases from the ileal tumor.

Diagnosis: Carcinoid or argentaffine tumor of the ileum with metastases to the liver and lymph nodes.

Result: Death from bronchopneumonia.

Comment: This case presents the unusual feature of two coincident, malignant tumors of different types. One may safely assume this to be true in view of the morphology of the neoplasms and their reaction to special stains. Apparently neither tumor affected the other in its course of growth and development save that the symptoms of the bronchial carcinoma masked any possible manifestation of gastro-intestinal pathology, thereby allowing the latter condition to go unrecognized until autopsy. It is difficult to

1 Material furnished by courtesy of Dr. MacCallum.
predict how long the intestinal tumor would have escaped recognition, but at its apparent slow rate of growth, several months would no doubt have elapsed before obstruction was produced.

It is interesting to note the relatively small size of the original tumor in spite of the fact that metastases were widespread. This is apparently a characteristic of the carcinoids and is no doubt responsible for the common failure to recognize the tumor early in its course.

CASE 12 (PATH. NO. 47522; CASE OF DR. E. S. BULLOCK): Clinical Features: R. W., a white female sixteen years of age, entered the hospital complaining of pain in the right side. The symptoms began forty-eight hours before admission with epigastric distress which soon led to nausea and vomiting. Shortly afterward the patient noticed a dull, aching pain in the right lower quadrant, which continued unabated and with increasing severity. She vomited several times before admission and lost all desire for food. The bowels had been normal in habit and the stools normal in consistency.

The patient was evidently ill but in no acute distress. Palpation of the abdomen elicited moderate tenderness in the right lower quadrant, but no masses could be outlined. The temperature was slightly elevated and there was a moderate leukocytosis. Appendicitis was diagnosed and operation advised.

Operation (February 1932): On opening the abdomen the operator found an appendix of approximately normal size, which was moderately inflamed at the tip. Near the end was a firm subserous nodule which was apparently occluding the lumen and had produced a bulbous dilatation of the tip. There were smaller nodules at the base of the appendix and on further examination several more were found scattered over the terminal ileum and cecum, while those two portions of bowel were partially adherent. Some of the nodules were confluent, others discrete. The condition was obviously malignant. The terminal ileum and the cecum were resected, together with the appendix, and a lateral anastomosis was made between the ileum and transverse colon. As far as could be ascertained, the mesenteric nodes were not involved.

The patient recovered from the operation without complications and was discharged improved.

Gross Pathology: The gross specimen consisted of the terminal ileum, appendix, and cecum. The appendix was moderately inflamed at the tip. Beneath the serosa could be seen a yellowish nodule about one centimeter in diameter, which had practically occluded the lumen of the viscus. Other smaller nodules were found in the body of the organ and near the base. In the walls of the cecum and ileum were several nodules of the same type, varying in size from a pea to a cherry. Some of these were confluent, others discrete. They were located in the wall but were not definitely attached to the mucosa, where they were also visible as small elevations. All of these secondary tumors had a yellowish tint on section.

Microscopic Pathology: Specimens from various of the secondary nodules identified them as part of the process. The tumor was composed of discrete nests and strands of cells fairly uniform in size and showing very few mitotic figures. The cytoplasm was abundant and granular. The groups of tumor cells were separated by a dense stroma consisting of hypertrophied connective tissue. The muscular part of the wall was invaded and infiltrated, although the serosa and mucosa remained intact. Sections stained by the silver impregnation method showed the affinity of the granules for silver.

Diagnosis: Carcinoid or argentaffine tumor of the appendix with metastases to the cecum and ileum.

Result: Patient well after six months.
Comment: This case was unique in that it was the only one of a large group of appendiceal carcinoids which had metastasized. Due to the somewhat isolated location of the appendix, metastases from malignant tumors occur late and, as in this case, are usually local. The gross form assumed by the secondary growths was peculiar and suggests an implantation metastasis. It is not, of course, proved beyond doubt that the appendix was the seat of the primary tumor. The greater prevalence of carcinoids in this region, however, and the infrequency of secondary growths, point toward it as the site of the initial tumor.

The presence of a tumor in the appendix is frequently made manifest by the symptoms of appendicitis. This is fortunate for both patient and surgeon, for by this means the tumors are recognized in an early stage and the prognosis is accordingly improved. This no doubt accounts for the rarity of advanced malignant appendiceal carcinoids.

CASE 29 (PATH. NO. G-10562):  
CLINICAL FEATURES: R. T., a colored male aged fifty-three, entered the clinic on July 3, 1928, complaining of nausea and vomiting of two weeks' duration. He was treated in the hospital dispensary but returned three weeks later with symptoms of increased severity. The discomfort had progressed to pain, at first intermittent, then constant but without radiation, and there was a constant sense of fullness in the epigastrium. Constipation was persistent. The patient had lost several pounds in weight, was easily fatigued, and had no desire for food.

There was a palpable mass in the abdomen with a sharp edge reaching below the umbilicus. It was hard, nodular, and tender and was thought to move with respiration. The blood picture revealed a marked secondary anemia with a hemoglobin value of 50 per cent and a red cell count of 3,700,000. The leukocytes numbered 12,000. The stools were positive for occult blood on one occasion only. The clinical impression was inoperable carcinoma of the liver, probably secondary to carcinoma of the stomach, and no operative procedure was advised.

The patient rapidly grew worse. Cachexia advanced and death occurred from inanition on Sept. 11, 1928, nearly two months after admission.

GROSS PATHOLOGY: At autopsy several hard, yellowish nodules were seen in the liver, varying in size from a pea to a marble. Some of these were discrete, others confluent. The stomach was apparently free from pathology. A small, ragged, ulcerated tumor was found in the large bowel at the sigmoid flexure. This was located chiefly in the submucosa, although the entire thickness of the bowel wall was apparently more or less involved, and the mucosa was ulcerated. On section the submucosa was seen to be infiltrated for some distance beneath the mucosa. The entire tumor measured about $2 \times 4$ cm. The color was brownish yellow. Several enlarged nodes in the mesentery had the appearance of metastases. During the routine examination of the lungs nodules were found which in every respect resembled the original tumor and the other metastases.

MICROSCOPIC PATHOLOGY: The growth in the colon, regarded as the primary tumor, did not at all resemble microscopically the usual type of bowel carcinoma. It was composed of broad strands and compact nests of cells surrounded and isolated by a dense, fibrous connective-tissue stroma. The cells were polygonal in shape, in contradistinction to the cylindrical cells characterizing adenocarcinoma. They con-

*Material furnished by courtesy of Dr. MacCallum.
Carcinoid Tumors of Gastro-Intestinal Tract

Tained a moderate amount of granular cytoplasm and small uniform nuclei filled with chromatin particles. In some portions of the tumor, especially near the borders, the cells were arranged in rosettes which faintly resembled the alveoli of adenoacarcinoma. No evidence of secretory activity could be made out.

The sections of the suspected lymph glands and the nodules from both the liver and the lungs contained tumor cells identical with those of the bowel tumor. When stained by the silver impregnation method, the granules showed a marked affinity for silver, thereby establishing the argentaffine nature of the tumor.

Diagnosis: Carcinoid or argentaffine tumor of the sigmoid colon with metastases to the regional lymph nodes, liver, and lungs.

Comment: It is worthy of note that, although the primary tumor must have been present for a considerable length of time as evidenced by the extent of the metastases, the duration of severe symptoms was relatively short. Furthermore, these symptoms were not primarily indicative of gastro-intestinal pathology, certainly not of a lesion of the colon. This again emphasizes an important clinical point with regard to the carcinoids, mentioned above. Not infrequently the primary carcinoid tumor is asymptomatic, and the onset of constitutional symptoms coincides with the occurrence of distant metastases.

The location of the primary growth in this case may seem to some a matter of question. Grossly this may have been difficult to ascertain. The typical cellular morphology, however, together with the characteristic staining reaction, positively identified the primary tumor as an intestinal carcinoid.

Case 28 (Path. No. 48429; Case of Dr. Dean Lewis): Clinical Features: A. B., a white female forty-six years of age, was admitted to the hospital on Oct. 20, 1930, complaining of attacks of abdominal pain, distention, and diarrhea. For several years she had been subject to attacks of dyspepsia which were variable in duration, intensity, and periodicity. The present attack differed from the preceding ones only in its slightly greater severity. The only relevant detail in the past history was an attack of pulmonary tuberculosis twelve years before, from which the patient had apparently recovered entirely.

A mass was palpable in the right lower quadrant of the abdomen, about the size of a lemon, freely movable, and non-tender. X-rays following a barium meal showed a dilated terminal ileum but no evidence of constriction. Following a barium enema, however, the x-rays revealed a large constricting filling defect in the cecum. This was diagnosed as a neoplasm, but in view of the past history of tuberculosis the possibility of an inflammatory mass was considered. Exploratory laparotomy was done.

Operation (Nov. 6, 1930): On opening the abdomen, a mass could be felt in the cecum, which was hard and freely movable. A few of the regional mesenteric nodes were enlarged and hard, but in spite of this the tumor was thought to be operable. The growth was resected together with a V-shaped piece of mesentery containing the enlarged nodes. An end-to-end anastomosis was then performed and the abdomen closed.

Convalescence was stormy, complicated by the development of a fecal fistula on the fifteenth day after operation. This drained freely for a time and finally closed three months later. The patient was discharged improved and when last heard from was perfectly well.
Gross Pathology: The specimen consisted of a resected portion of bowel six inches in length. In the center of this was an annular constricting tumor completely encircling the bowel but producing no elevation on the serosal surface. When the specimen was opened it was found that the tumor had partially occluded the lumen. The growth had apparently originated in the submucosa but had involved the entire bowel wall secondarily. The mucosa was intact over the surface. The cut section was firm in consistency and yellow in color. Attached to the resected mesentery were several enlarged lymph nodes. One of these was quite hard and when sectioned exhibited the same yellow color as the primary tumor.

Microscopic Pathology: The tumor was composed of densely packed cuboidal cells arranged in strands and compact groups. These were fairly uniform in size and possessed a moderate amount of granular cytoplasm. The granules stained dark brown or black with the silver impregnation technic, identifying the tumor as of argentaffine type. Occasional vacuoles could be seen near the bases of the cells. The stroma was quite dense and surrounded the nests of cells, leaving them as discrete islands of tumor tissue. A hyperfibrosis accompanied the metastases so that the normal structure was almost completely replaced by the tumor and its stroma.

Diagnosis: Carcinoid or argentaffine tumor of the cecum with metastases to the regional mesenteric lymph nodes.

Result: Patient well, three years; has gained 35 pounds and is symptom-free.

Comment: That the first pathologist examining the growth was misled into a diagnosis of adenocarcinoma may be explained in part by the presence of numerous pseudo-alveoli in the edges of the tumor but largely by the rarity of carcinoid tumors in the colon. The yellow color, however, is not typical of carcinoma. Furthermore, the microscopic arrangement of the cells, while not absolutely conclusive, is so characteristic that after observing a number of carcinoids one can hardly fail to identify the type even without recourse to special stains.

The gastro-intestinal history was vague, extending over a number of years, and it was practically impossible to ascertain the date of onset of the first relevant symptom. It would be unwise to attempt the diagnosis of a carcinoid tumor from the clinical history alone but, as suggested by the previous case, a tumor characterized by an insidious onset of vague gastro-intestinal symptoms and an unusual paucity of general symptoms prior to metastasis suggests a diagnosis of carcinoid.

The status of malignancy among the carcinoids cannot as yet be accurately evaluated, since so few cases have been thoroughly studied. Certainly the figures in Table I cannot be considered accurate for all cases. Malignant carcinoids of the appendix, for example, as proved by metastases, are extremely rare and the chance occurrence of one such case in this relatively small group of seventeen gives a much higher incidence than may be expected in a larger series. Similarly it cannot be said that all carcinoids occurring in the stomach and colon are malignant. The worth
of the table lies in its indication of the relative percentages of malignancy in various locations. There is reason to believe that it gives a fair impression of the relative occurrence of malignancy in the different portions of the bowel.

Morphologically it is impossible to differentiate the benign from the malignant tumors. The author is inclined to agree with Marangos and Gáspár in considering the carcinoids as potentially malignant tumors, but whose malignant characteristics are not apparent until late in the disease, as a result of their extremely slow rate of growth. Stewart and Taylor have called attention to the low grade of malignancy even after metastasis has taken place. They report a case in which large pelvic deposits secondary to a carcinoid of the appendix were removed, apparently effecting a cure. The tumors are, therefore, to be regarded as a source of danger and treated accordingly by surgical means. Appended is a list of the malignant carcinoids thus far reported in the literature (Table II).

Prognosis

The prognosis of carcinoid tumors depends upon their early recognition and the rate of growth. The so-called benign tumors commonly found in the small intestine are usually of little significance, growing slowly and seldom producing symptoms sufficient for their recognition before operation or post-mortem examination. Carcinoids located in the stomach or colon are more likely to be malignant. If the growth is of the constricting type or located where partial obstruction is brought on early, the condition may be recognized in time to obtain a good operative result. If not, the tumor passes unnoticed clinically until widespread metastasis has occurred and the prognosis is poor. The presence of appendiceal tumors is usually made manifest through symptoms of chronic appendicitis. Such tumors are as a rule recognized early and removed before metastasis has taken place. The mortality from carcinoids as compared with carcinomas, is, therefore, low and recurrences are rarely found.

Treatment

Surgical extirpation constitutes the only satisfactory means of treatment, and is similar to the treatment of any tumor in the gastro-intestinal tract, depending on the location. Resection is always to be preferred to local excision. In view of the relatively small number of cases and the consequent inexperience of radiologists, the efficacy of irradiation cannot be evaluated.
### TABLE II: Malignant Carcinoids from the Literature

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Reference</th>
<th>Location</th>
<th>Race</th>
<th>Sex</th>
<th>Age</th>
<th>Location</th>
<th>Metastases</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ransom</td>
<td><em>Lancet</em> 2: 1021, 1890</td>
<td>Small intestine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Liver</td>
<td>unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>10.</td>
<td>Dukes and Lockhart-Mummy</td>
<td><em>J. Path. &amp; Bact.</em> 29: 308, 1928</td>
<td>Ileum</td>
<td>W</td>
<td>F</td>
<td>76</td>
<td>Peritoneum, liver, nodes</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td></td>
<td>In Henke and Lubarsch, loc. cit.</td>
<td>Ileum</td>
<td>W</td>
<td>F</td>
<td>52</td>
<td>Lymph nodes</td>
<td>unknown</td>
<td>Well, three years</td>
</tr>
<tr>
<td>15.</td>
<td></td>
<td></td>
<td>Ileum</td>
<td>W</td>
<td>F</td>
<td>81</td>
<td>Lymph nodes, mesentery, ileum</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td></td>
<td></td>
<td>Ileum</td>
<td>W</td>
<td>M</td>
<td>41</td>
<td>Mesentery and lymph nodes</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td></td>
<td></td>
<td>Ileum</td>
<td>W</td>
<td>M</td>
<td>48</td>
<td>Lymph nodes</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Ritchie</td>
<td><em>Arch. Path.</em> 10: 855, 1930</td>
<td>Appendix</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Mesentery and liver</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>26.</td>
<td></td>
<td>Loc. cit.</td>
<td>Ileum</td>
<td>W</td>
<td>M</td>
<td>26</td>
<td>Lymph nodes</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>27.</td>
<td></td>
<td></td>
<td>Ileum</td>
<td>W</td>
<td>M</td>
<td>59</td>
<td>Lymph nodes</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

1. Twenty-nine cases of carcinoid tumors in the gastro-intestinal tract have been studied in this laboratory with regard to their clinical and pathological significance. Six of these were malignant and had metastasized to the regional nodes or the liver.

2. The origin of carcinoids has been a subject of much controversy. It is now generally conceded that they arise from the cells of Kulitschitzky or the argentaffine cells occurring in the normal intestinal mucosa. The origin and function of these cells remain a matter of speculation, but they are thought to be related in some way to the chromaffin system.

3. The pathology of the group is characteristic. Occurring most commonly in the appendix, the carcinoids are yellow, submucous tumors which encroach upon the lumen. Next in frequency in the small intestine, they form small submucous or pedunculated nodules which are usually asymptomatic and are not recognized clinically. Rarely found in the stomach and large intestine, they are of more significance. They are larger, and metastasis occurs in a greater number of cases. They are clinically not unlike adenocarcinomas save for general symptoms of less severity.

4. The histology of the carcinoids is typified by groups and columns of cells surrounded by a dense stroma of hypertrophied connective tissue and smooth muscle. The cells are small and regular in size, the granular cytoplasm having an affinity for silver. The nuclei are uniform and are heavily dotted with chromatin particles.

5. The prognosis of the group as a whole is good. Only in the minority of cases which have metastasized is the outlook grave. Even in such an event, if the tumor is recognized clinically before metastasis has become widespread, a good result may be attained through surgical intervention.

Abstracts of Cases

Stomach

Case 1 (Path. 40700): Reported in detail above.

Small Intestine


Case 3 (Path. 31805): Reported in detail above.


Appendix


CASE 12 (PATH. 47522): Reported in detail above.


CASE 14 (PATH. 47168): White female, aged twenty-eight. Carcinoid of tip of appendix. Symptoms: pain in side, abdomen, and back, becoming more acute and accompanied by nausea and vomiting. Signs: acute pain, tenderness, and

* Case previously reported by Forbus.


Case 24 (Path. 31301): White female, aged thirty-three. Carcinoid of tip of appendix. Pain referred to left iliac region followed by nausea and vomiting.

4 Case previously reported by Forbus.


Colon

Case 28 (Path. 49429): Reported in detail above.

Case 29 (Path. G-10562): Reported in detail above.

Bibliography


Masson, P.: Carcinoids (argentaffin-cell tumors) and nerve hyperplasia of the appendicular mucosa, Am. J. Path. 4: 181, 1928.


Mering: * Quoted by Forbus.


* Case previously reported by Forbus.

* Original article not obtainable.
Carcinoid Tumors of Gastro-Intestinal Tract

Ransom, W. B.: Primary carcinoma of the ileum, Lancet 2: 1020, 1890.


Cordier, R.: Les cellules argentaffines dans le tumeurs intestinales, Arch. internat. de med. exper. 1: 59, 1924.

