ARGEN TAFFINE TUMORS
REPORT OF EIGHTY-FOUR CASES; THREE WITH METASTASES

JOSEPH E. PORTER, M.D., AND CHARLES S. WHelan, M.D.

(From the Mallory Institute of Pathology and the First Surgical Service of the Boston City Hospital, Boston, Mass.)

Argentaffine or carcinoid tumors of the appendix are not rare, occurring about once in every 200 to 500 appendices removed at operation. They are seen less frequently in the small bowel and rarely in the large bowel, stomach, or duodenum.

Because of their similarity to carcinoma and the nature of the cells involved, argentaffine tumors have been a source of much interest and speculation. Lubarsch (1888) regarded them as atypical primary carcinomata. Ransom in 1890 reported the first malignant argentaffinoma originating in the ileum and metastasizing to the liver. When Oberndorfer in 1907 suggested the name "carcinoid" for tumors of this group, he made it clear that he believed them to be entirely benign. He was the first to point out the chromaffinity of the tumor cells and he demonstrated doubly refractile bodies in their cytoplasm. Hübischmann (1910) considered these tumors different from those usually seen in the intestinal tract, because of their yellow color. He believed that they arose from the "yellow cells" of Schmidt. Bunting (1904) and Burchhardt (1909) emphasized their resemblance to basal-cell carcinomata, and Krompecher (1919) believed that they arose from the cells in the mucosa of the gastro-intestinal tract in much the same manner that basal-cell carcinomata arise in the skin. Trappe (1907) regarded them as pancreatic rests, while Saltykow (1912), influenced by their endocrine-like structure, believed them to be derived from remnants of the pancreatic islets. The islet cells, however, do not reduce silver (Fig. 1), do not have a granular cytoplasm, and contain no doubly refractile lipid.

Gosset and Masson in 1914 showed quite clearly that the cells were argentophiile and represented downgrowths from the bases of the crypts of the appendiceal mucosa. More recently Masson (1930) has called attention to the relation of these tumors to nerves and muscle.
Table I: Extra-appendiceal Carcinoids

<table>
<thead>
<tr>
<th>Patient</th>
<th>Path. number</th>
<th>Sex and age</th>
<th>Primary tumor</th>
<th>Metastases</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. M. R.</td>
<td>A-34-587</td>
<td>F 64</td>
<td>Duodenum</td>
<td>None</td>
<td>Death due to bronchopneumonia, cirrhosis of liver. Found at autopsy.</td>
</tr>
<tr>
<td>3. C. C.</td>
<td>A-35-139</td>
<td>F 60</td>
<td>Ileum</td>
<td>None</td>
<td>Death due to cirrhosis of liver, bronchopneumonia. Found at autopsy.</td>
</tr>
<tr>
<td>7. J. C.</td>
<td>A-36-357</td>
<td>M 51</td>
<td>Jejunum</td>
<td>None</td>
<td>Death due to cerebral hemorrhage, bronchopneumonia, hypertensive heart disease. Found at autopsy.</td>
</tr>
</tbody>
</table>

Material

In a review of the pathological material at the Boston City Hospital from 1910 to 1937 inclusive, there were found 72 argentaffinomas of the appendix in a group of 26,384 appendices removed surgically (0.28 per cent). In the same period there were seen 2 argentaffine tumors of the stomach, 1 of the gallbladder, 1 of the duodenum, and 8 of the small bowel.\(^1\)

None of the appendiceal tumors was malignant. Of the 8 small bowel

---

\(^1\) One of the small bowel tumors was discovered at autopsy April 5, 1938.
argentaffinomas, 3 were malignant, of which 2 were found post mortem and 1 was removed at operation. The stomach, gallbladder and duodenal cases were all benign.

The 12 extra-appendiceal cases are listed in Table I. The histories of the malignant cases follow.

**Case Histories: Malignant Carcinoids**

**Case 1.** Argentaffinoma of the terminal ileum with metastases to the mesentery:

R. L., a thirty-seven-year-old man, was admitted Aug. 29, 1928, complaining of constipation of one year's duration with considerable gas, flatus, and belching, and of dull pain and a mass in the right lower quadrant for six months. Five months before entry he had begun to have diarrhea and this had alternated with constipation for three months. He had become progressively weaker and had lost 15 pounds in weight.

![Fig. 1. Case 11. Photomicrograph of Pancreas, Stained According to Masson's Method of Silvering in Block](image)

Note the pancreatic islet in the center. These cells have not reduced the silver while the adjacent metastatic tumor cells have.

The patient was fairly well developed but poorly nourished. Examination showed visible peristalsis and a tender nodular mass in the right lower quadrant, about 8 cm. in diameter, firm and slightly movable. The blood and urinary findings were normal. The Kahn test was negative, and repeated guaiac tests revealed no occult blood in the stools. The admission diagnosis was carcinoma or tuberculosis of the cecum.

Roentgen examination following a barium enema six days after admission showed no abnormality of the large bowel. The chest plate showed slight infiltration at the right apex and bronchiectasis at the right base. The gastro-intestinal series revealed spastic colitis, consistent with tuberculosis of the cecum.

Operation was performed on Sept. 17, 1928, by Dr. Irving Walker. The terminal ileum was found to be distended and bound down posteriorly to a mass of nodes in the base of the mesentery, causing practically complete obstruction. There was an indurated area at one point in the ileum. About 3 feet of intestine were resected, and a lateral anastomosis between the ileum and the transverse colon was done, the blind ends of the ileum being inverted. An enterostomy was made in the ileum just proximal to the anastomosis. A rubber drain was inserted through a stab incision in the right flank. The patient is well ten years later.
Pathology: The specimen consisted of a segment of small intestine, 36 inches in length, the loops of which were drawn into a knot-like mass by tumor, which had markedly contracted the mesentery. On opening the intestine numerous yellowish white, firm, submucosal bodies, averaging 2 mm. in diameter, were encountered. The largest nodule, 0.5 cm. in diameter, was sharply demarcated. There was one ulcerated area 1 cm. in diameter and 0.2 cm. deep, the edges of which were undermined. The mesentery was thicker and firmer than normal and showed an increase in scar-like tissue. One lymph node measured 0.5 cm. in diameter and contained tumor and some calcium. Tumor tissue also surrounded a blood vessel 3 mm. in diameter. Sections from the intestine showed sheets and masses of polygonal cells characteristic of argentaffine tumors. In the mesentery were scattered masses of tumor cells surrounding numerous nerves. The tumor tissue reduced an ammoniacal solution of silver (Fig. 2).

Microscopic Diagnosis: Carcinoid of terminal ileum with metastases to mesentery.

FIG. 2. CASE 1. TUMOR TISSUE SHOWING FINE BLACK GRANULES IN CYTOPLASM

Masson’s method of staining in block was used on tissue that had been fixed in 10 per cent formalin for approximately nine years.

CASE 11. Argentaffinoma of the ileum and appendix with implants on the serosa of the intestine, diaphragm, mesentery and omentum; metastases to the liver, peri-aortic, hepatic, and pancreatic lymph nodes, vertebral marrow, and adrenals:

S. P., a sixty-five-year-old man, was admitted on April 12, 1937. Four months previously he had begun to suffer from anorexia and constipation relieved by catharsis. In the interval he had experienced sharp pain in both lower quadrants after meals. He had had nocturia for four months and had lost 40 pounds in the past four years.

The patient was well developed and fairly well nourished. A firm mass about 6 cm. in diameter was found in the right para-umbilical region, and another was felt high in the rectum. The blood pressure was 135/80. Laboratory findings were not significant. The admission diagnosis was carcinoma of the ascending colon. A barium enema showed a constricted area in the rectosigmoid consistent with carcinoma.

Under spinal anesthesia a laparotomy was done two days after entry, by Dr. Arthur Kimpton. A considerable amount of thin, blood-tinged fluid was found in the abdomen. The omentum, mesentery and bowel were diffusely studded with metastatic implants. The cecum and rectosigmoid were bound together in the right lower quadrant. The liver contained large metastatic masses. A nodule on the mesentery was removed for diagnosis and the abdomen was closed without drainage. Because of the matting together of the bowel it was impossible to determine the origin of the tumor.

The patient died twelve days after operation.

Clinical Diagnosis: Carcinoma of the rectosigmoid; generalized abdominal metastases.

Autopsy: The abdomen contained 1500 c.c. of cloudy, pale green, foul-smelling fluid. There was moderate distention of most of the small bowel, which was covered with thick
masses of fibrinopurulent exudate. The serosal surfaces throughout were studded with tumor nodules from 0.1 to 0.5 cm. in diameter. Tumor nodules were also found in the mesentery and the omentum, measuring up to 2 cm. in diameter. The liver edge was 8 cm. below the xiphoid and 5 cm. below the costal margin in the mid-clavicular line. The surface of the organ was studded with numerous nodules up to 3 cm. in diameter. The diaphragm was also infiltrated with tumor nodules, more numerous on the right.

The small intestine showed numerous implants, especially along the mesenteric border. Ten centimeters from the cecum, some four loops of ileum were bound together by fibrous proliferation about the tumor tissue in the mesentery. The lumen here was much narrowed (Fig. 3). The bowel showed moderate torsion and was filled with bright red blood. Above this point the intestine was moderately dilated, while below it presented a normal caliber. There was a submucous yellow tumor nodule 2 cm. in diameter in the ileum where the loops had become adherent. Small implants were present on the serosal surface of the colon, but the mucosa was negative. The lumen of the appendix was obliterated by firm, fibrous tissue and there was a narrow rim of yellow tissue in the muscularis.

The pancreas was somewhat smaller than normal. On section the body and the tail were found to be almost entirely replaced by firm, white, smooth tumor.

The liver weighed 3000 gm., about twice the normal size. The surface was studded with firm, whitish-yellow, umbilicated, nodules up to 3 cm. in diameter. On section similar nodules were found scattered through the organ and there was a marked diminution in the amount of normal intervening liver parenchyma. Several tumor-containing lymph nodes were present about the porta of the liver.

Microscopic Examination: The wall of the ileum was partially replaced by tumor and the surface, while not ulcerated, was covered by fibrous tissue and a thin rim of mucosal epithelium. The cells were arranged in small masses and sheets separated by dense connective tissue. Occasional clusters of cells formed a rosette with a lumen in the center. In such instances the cells were columnar; elsewhere they were polyhedral and the cell boundaries were difficult to make out. In one instance the cells were surrounded by mucinous material. The nuclei were round or slightly ovoid with a fine chromatin network. Occasionally a giant cell was present. No mitoses were found.

The lumen of the appendix was obliterated and the wall was almost completely replaced by dense fibrous tissue, in which small clumps of tumor cells were seen. In places the muscularis was still preserved.
A section of the mesentery taken near the tumor in the ileum showed dense fibrous tissue infiltrated with large masses of tumor cells, many in lymphatics.

The pancreas was occupied in part by large sheets of metastatic tumor cells, which were irregularly invading the adjacent tissues. The cells were uniform in size and shape and resembled the tumor in the intestine.

The liver contained large areas of metastatic tumor, in part encapsulated and compressing the adjacent liver cells, elsewhere infiltrating the liver tissue after extending through the capsule. Numerous small clumps of 6 to 12 tumor cells were seen lying free in the sinuses (Fig. 4).

There were several small clumps of tumor cells in the bone marrow of a lumbar vertebra. The marrow elements showed normal maturation.

A few tumor cells were seen in the periadrenal fat.

Specimens of the primary tumor and of the hepatic and pancreatic metastases reduced an ammoniacal solution of silver (see Figs. 1 and 4).

**FIG. 4. CASE 11. HIGH-POWER PHOTOMICROGRAPH OF TUMOR CELLS IN THE LIVER, STAINED ACCORDING TO MASSON'S METHOD OF SILVERING IN BLOCK**

The cytoplasm is filled with reduced silver granules.

**CASE 12. Argentaffinoma of ileum with metastases to the mesentery; hypertensive heart disease; malignant nephrosclerosis.**

T. R., a sixty-one-year-old man, was admitted on March 26, 1938, having been advised to enter a hospital by his oculist. The history was unreliable. The patient had suffered for years from constipation, which had grown worse in the past three months. He had lost 18 pounds in weight during the last year. He was well developed and well nourished, not acutely ill but sluggish mentally. He became increasingly drowsy and comatose and died ten days after admission. The clinical findings were characteristic of essential hypertension, hypertensive retinopathy, benign nephrosclerosis, and uremia.

**Autopsy:** In the intestine, 3 cm. proximal to the ileocecal valve, was a firm oval tumor measuring 3 X 2 cm., projecting into the lumen. It was covered by mucosa, which was not ulcerated. A longitudinal section (Fig. 5) showed a pale yellow color with an apparently normal muscular layer. The tumor had infiltrated through the serosal surfaces which had become adherent, forming a U-shaped kink. The adjacent mesentery contained a small tumor 5 mm. in diameter.

**Microscopic Examination:** The tumor consisted of uniform, closely packed cells arranged in small masses surrounded by thin fibrous stroma. There were no mitoses. Some
of the cells were arranged in small rosettes, sometimes about a small droplet of mucus. The
musculature showed invasion by thin strands of cells migrating toward the serosa, where a
fair-sized mass of tumor cells was seen. Sections through the mesentery showed masses of
tumor cells surrounding the vessels and growing in the perineural lymphatics. One lymph
node in the mesentery was also replaced by tumor. Masson's technic of silvering in block
showed black granules in the cells.

INCIDENCE

In the 2922 autopsies performed at the Boston City Hospital from 1934 to
1937 inclusive, 10 argentaffine tumors were found, an incidence of 0.34 per
cent. Humphreys reports the presence of 8 argentaffinomas in 3200 autopsies,
an incidence of 0.25 per cent. Raiford found 29 argentaffine tumors in 1611
tumors of the gastro-intestinal tract from the Johns Hopkins Hospital, or 1.8
per cent.

From 0.2 per cent to 0.5 per cent of appendices removed at operation will
be found to contain argentaffine tumors. Of the 26,384 appendices removed
at the Boston City Hospital from 1914 to 1937 inclusive, 72, or 0.28 per cent,
contained argentaffinomas. Smith found 21 argentaffinomas in 7865 surgically
removed appendices at the Free Hospital for Women, an incidence of 0.26 per
cent. The figures given by other observers for the frequency of argentaffine
tumors in surgically removed appendices are: Forbus, 0.4 per cent; Jones, 0.2
per cent; Oates, 0.3 to 0.4 per cent; Price, 0.4 per cent.

Argentaffine tumors are seen almost twice as frequently in the appendix as
in the small bowel. When occurring in the small bowel, these tumors have a
predilection for the terminal ileum. Cooke, in 1931, collected from the litera-
ture a total of 104 argentaffinomas of the small intestine. Of 92 cases in
which the location was clearly stated, 79 were in the ileum, and of these 61
were in the lower ileum. Argentaffinomas in other parts of the gastro-intesti-
nal tract than the appendix and small bowel are rare, though they have been
reported at all levels. Raiford and Bailey have each reported an argentaffi-
noma of the stomach. Our series includes 2 such cases. Our case and that of
Joël appear to be the only argentaffinomas of the gallbladder on record. Duodenal tumors are described by Raiford, Semsroth, Wolfer, and the present authors. Argentaffinomas of Meckel's diverticulum have been observed by Price, Stewart and Taylor, Hertzog and Carlson (2 cases), and Hicks and Kadinsky. Stewart and Taylor, however, believed that the tumor described by Hicks and Kadinsky was not an argentaffinoma, but ectopic gastric mucosa in Meckel's diverticulum. Raiford and Wyatt report cases in the cecum. Saltykow in 1912 published 2 cases of colonic argentaffinoma. Other colonic cases have been listed by Raiford, Brunschwig, and Humphreys.

The age incidence of appendiceal argentaffinomas is lower than that of argentaffinomas in the small bowel. Stewart and Taylor claim that the heaviest incidence of the appendiceal tumors is in the third decade, whereas the small intestine is more frequently involved in the fourth and fifth decades. In Raiford’s series of 29 argentaffinomas of the gastro-intestinal tract the appendiceal tumors occurred at an average age of twenty-five years, while the average age for argentaffinomas of the small bowel and colon was fifty-five and forty-five years respectively. The average age of 20 of Cooke’s 21 patients with malignant carcinoids of the small bowel was 57.2 years. Sixty-eight of the 83 benign cases averaged 54.3 years. Among 48 malignant argentaffinomas of the small bowel collected to date, the ages of 37 patients are definitely stated. These are as follows:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 30</td>
<td>2</td>
</tr>
<tr>
<td>30 to 40</td>
<td>0</td>
</tr>
<tr>
<td>40 to 50</td>
<td>6</td>
</tr>
<tr>
<td>50 to 60</td>
<td>12</td>
</tr>
<tr>
<td>60 to 70</td>
<td>11</td>
</tr>
<tr>
<td>70 to 80</td>
<td>4</td>
</tr>
<tr>
<td>80 to 90</td>
<td>2</td>
</tr>
</tbody>
</table>

Twenty-three of the 37 cases are seen to fall in the sixth and seventh decades. The explanation for the earlier age incidence of the appendiceal cases seems to be the tendency of these tumors to be associated with inflammatory changes, requiring early surgical intervention. Argentaffinomas of the small bowel, on the other hand, develop so gradually that they cause few and rather late symptoms.

Of 49 patients with malignant argentaffinoma 26 were males and 23 females. The general impression is that the tumor occurs with about equal frequency in the two sexes.

**CLINICAL PICTURE**

We know of no instance of an argentaffinoma having been diagnosed preoperatively. Argentaffinomas of the appendix may be discovered at operations for appendicitis or in appendices incidentally removed. The rest are found post mortem. There is nothing distinctive about the symptoms produced by an appendiceal argentaffinoma, but we should immediately think of this possibility upon discovering a tumor in the appendix.

The outstanding clinical manifestation of argentaffinoma of the small bowel is intestinal obstruction. Cooke has stated that this occurs in about 50 per
cent of malignant argentaffinomas of the small intestine. Of the 152 examples collected by Humphreys, 36, or 24 per cent, had produced symptoms of obstruction. Two of the three patients in our series were operated upon for intestinal obstruction.

The patient may give a history of constipation for a year or two, recently becoming more obstinate with attacks of abdominal pain and vomiting. One of our patients (R. L.) had had obstructive symptoms for one year before operation. Bailey's patient had intermittent constipation with nausea and vomiting for two years, and in Christopher's case there were recurrent attacks of abdominal pain for three years. The stools usually show no occult blood. This is explained by the fact that the intestinal mucosa is usually intact over these tumors. The stool examinations in our first case were repeatedly negative for occult blood. Another of our patients (S. P.) had a large primary tumor obstructing the ileum, but the overlying mucosa showed no ulceration.

We may suspect the presence of an argentaffine tumor of the small bowel in a patient of middle age with chronic intestinal obstruction, without occult blood in the stools, but with obstruction in the terminal ileum demonstrable roentgenographically. If argentaffinoma of the small bowel is to be recognized at operation it must first of all be kept in mind. Such recognition is important. Realizing that the prognosis of argentaffine tumors is better than that of carcinoma, and that a patient may live for years with residual tumor tissue without showing ill effects, we can feel justified in taking radical measures in a case which otherwise would seem to be too far advanced for such treatment.

DEGREE OF MALIGNANCY AND PROGNOSIS

It is safe to say that argentaffinomas are potentially malignant. If allowed to grow unmolested they eventually break through their barriers and infiltrate the mesentery. From this point onward they may metastasize to lymph nodes, liver, or both. Most of them, however, seem to be of low grade malignancy and undoubtedly require a long time to metastasize. Gásspár would have them classified as true carcinomas, stating that their proliferation is slow, but the formation of metastases is only a question of time. Humphreys feels that the threat of possible malignancy is inherent, but that only when the slowly growing argentaffinoma reaches a relatively large size and infiltrates all of the bowel wall is there any likelihood of metastases.

Argentaffinomas of the small bowel have greater malignant possibilities than those originating in the appendix. As stated before, one factor may be the earlier surgical intervention in appendiceal argentaffinomas because of their association with appendicitis. In 1934, Humphreys reported that 37 (24.4 per cent) of the 152 small bowel carcinoids collected from the literature had metastasized. There is no comparable figure for appendiceal argentaffinomas, but it would certainly be much lower.

Formerly argentaffinomas were considered to be perfectly benign. Ransom in 1930 reported the first malignant case, originating in the ileum and metastasizing to the liver. Stewart and Taylor in 1926 reported 18 argentaffinomas with metastases. In 1931 Cooke found 21 malignant argentaffinomas


Table II: Malignant Argentaffinomas, Supplementing Wyatt’s Table (46).

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex and age</th>
<th>Primary tumor</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasegawa (15)</td>
<td>F 49</td>
<td>Appendix</td>
<td>Regional lymph nodes and liver</td>
</tr>
<tr>
<td>Gibitz (14)</td>
<td>F 69</td>
<td>Appendix</td>
<td>Pleura and liver</td>
</tr>
<tr>
<td>von Rehren (37)</td>
<td>M 86</td>
<td>Small intestine</td>
<td>Mesentery, peritoneum, liver hilus, and diaphragm</td>
</tr>
<tr>
<td>Windholz (44)</td>
<td></td>
<td>Appendix</td>
<td>Mesentery</td>
</tr>
<tr>
<td>Barth (3)</td>
<td></td>
<td></td>
<td>Regional lymph nodes; ovary (?)</td>
</tr>
<tr>
<td>Planson (34)</td>
<td>M 60</td>
<td>Ileum</td>
<td>Inguinal node</td>
</tr>
<tr>
<td>King (21)</td>
<td>F 51</td>
<td>Ileum</td>
<td>Ileocecal nodes</td>
</tr>
<tr>
<td>Carr (8)</td>
<td>M 55</td>
<td>Ileum</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>Stout (42)</td>
<td>M 57</td>
<td>Ileum</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>Bailey (1)</td>
<td>M 54</td>
<td>Ileum</td>
<td>Mesentery; invasion of liver</td>
</tr>
<tr>
<td>Bailey (1)</td>
<td>M 57</td>
<td>Ileum</td>
<td>Mesentery</td>
</tr>
<tr>
<td>Lewis and Geschickter</td>
<td>M 60</td>
<td>Appendix</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>Cabot Case *</td>
<td>F 64</td>
<td>Ileum</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>Cabot Case 20342 (6)</td>
<td></td>
<td>Ileum</td>
<td>Mesentery</td>
</tr>
<tr>
<td>Gierlich (13)</td>
<td>71</td>
<td>Ileum</td>
<td>Retroperitoneal nodes, liver, pancreatic, perihepatic, periportal lymph nodes</td>
</tr>
<tr>
<td>Knauer (22)</td>
<td>M 52</td>
<td>Ileum</td>
<td>Regional lymph nodes, liver, spine with compression of spinal cord</td>
</tr>
<tr>
<td>Cabot Case 22511 (7)</td>
<td>F 22</td>
<td>Appendix</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>Authors’ Case 1</td>
<td>M 37</td>
<td>Ileum</td>
<td>Mesentery</td>
</tr>
<tr>
<td>Authors’ Case 11</td>
<td>M 65</td>
<td>Ileum and appendix</td>
<td>Implants on serosa of intestine, diaphragm, mesentery and omentum; metastases to liver, periarterial, hepatic and pancreatic lymph nodes, bone marrow, and adrenals</td>
</tr>
<tr>
<td>Authors’ Case 12</td>
<td>M 61</td>
<td>Ileum</td>
<td>Mesentery</td>
</tr>
</tbody>
</table>

* Case cited by Mallory in discussion of Cabot Cases 20342 and 22511 (6, 7).

of the small bowel in the literature and added 3 more. Raiford in 1933 brought the total of malignant argentaffinomas to 34. Wyatt raised this number to 46 in 1938. We have succeeded in bringing the total of malignant argentaffinomas to 67, finding in our review of the literature 18 cases that had not been included by Wyatt and contributing 3 new malignant cases. These 21 cases are presented in Table II, which supplements Wyatt’s table (46).

Although it is now generally known that argentaffinomas are potentially malignant, their grade of malignancy is usually quite low. This means a better prognosis than in carcinomata. The following cases are illustrative.

In 1913, Dr. Daniel F. Jones operated for an obstructing argentaffine tumor of the ileum, with a large retroperitoneal metastatic mass closely associated with the root of the mesentery. The segment of ileum was resected and an end-to-end anastomosis was done, no attempt being made to resect the mesenteric mass. The patient recovered. Twenty years later death occurred from
an unrelated condition, and at autopsy a mass was found in the base of the distal third of the mesentery of the small bowel, obviously the same mass that had been observed twenty years before.²

Stewart and Taylor report a malignant argentaffinoma of the appendix with metastases to the pelvis. The patient was alive and well ten years and nine months after operation, which consisted in the removal of the primary and secondary growths.

Our first patient (R. L.) was operated upon in 1928 because of intestinal obstruction. The lesion was located in the terminal ileum and the loops of intestine in this region were bound down to a mass of involved nodes at the base of the mesentery. Resection was done, followed by ileo-transverse co-lostomy. Several involved lymph nodes at the base of the mesentery had to be left, but when last seen (almost ten years after operation) the patient was well and apparently free of disease.

TREATMENT

The treatment of argentaffinomas of the gastro-intestinal tract is surgical. An obviously benign argentaffinoma of the appendix is treated by appendectomy. When mesenteric metastases have occurred, resection of the tumor-bearing portion of the mesentery is necessary.

In dealing with argentaffinomas of the small bowel it is important to remember their predilection for the terminal ileum and their tendency to be multiple and to produce obstruction. The treatment of these tumors is the same as that of carcinoma. Resection must be performed, including a generous amount of mesentery. Adjacent bowel suspected of containing another tumor or tumors should be included in the resection.

THE ARGENTAFFINE OR CHROMAFFINE CELLS

Heidenhain, in 1870, was the first to describe the "chromaffine" reaction in certain cells of the gastric mucosa. Such cells have since been shown to be identical with those occurring in the so-called carcinoid or argentaffine tumors of the gastro-intestinal tract. These cells have a multiplicity of characteristics and because of this, various names have been attached to them, depending upon the particular property observed by the investigator. Nussbaum in 1879, for example, noted the affinity of these cells for osmic acid and used the term osmiophile cells. Nicolas in 1890 and Kultschitzky in 1897 described cells with acidophilic granules in the crypts of the intestine. Schmidt in 1905 observed in some of the cells in the mucosa of the intestine after fixation in solutions containing chrome salts the presence of yellow granules. Such cells he called gelben Zellen. Gosset and Masson in 1914 demonstrated the affinity of these cells for silver. It is thus readily understandable why they are known by such diverse names as yellow cells of Schmidt, the enterochromaffine cells of Ciaccio, the argentaffine cells of Masson, and chromo-argentaffine cells of Cordier.

Argentaffine cells have been observed in practically the entire gastro-intestinal tract including the gallbladder and ducts of the pancreas. Peyron

² This case is cited by Mallory in the discussion of Cabot Cases 20342 and 22511 (6, 7).
in 1924 saw cells in the liver with silver granules and thought they were similar to those in the intestine. The granules, however, in the liver cells are coarser and probably represent bile. Parat in 1924 and Masson in 1928 reported that in human material the argentaffine cells appear at about the fourth or fifth month, but Patzelt in 1931 found them in human embryos as early as the twelfth week. Simard and Van Campenhout reported that in chicks they are not seen before the eleventh day of incubation.

GROSS AND MICROSCOPIC APPEARANCE OF TUMORS

The gross appearance of these tumors is quite characteristic and constant. In the appendix they usually occur in the tip, which is generally obliterated and shows a bulbous swelling. The overlying serosa is pale and smooth. The cut surface of the tumor is of a pale yellow color with delicate whitish gray interlacing strands of tissue, varying with the amount of neurinomatous proliferation. Not infrequently the tumors grow as small submucosal nodules. The larger ones, either benign or malignant, are quite distinctive and infiltrate the muscularis, which is usually quite well preserved. Where the tumor has extended through the serosa, adhesions between adjacent surfaces produce a knuckling (Figs. 3 and 5) or kinking of the bowel which leads to obstruction. This is an important point in the differentiation of argentaffinoma from carcinoma, which instead of obstructing by kinking the wall, narrows the lumen by annular constricting growth. Secondary implants or metastases produce marked adhesions between serosal surfaces elsewhere.

Argentaffine tumors are composed of polyhedral cells, many appearing round. The cell boundaries are often indistinct unless the tissue has been well preserved. The shape varies, especially in the normal gastro-intestinal mucosa, depending to a great extent upon the compression by adjacent cells. In the base of the crypt the cells are often triangular, though cylindrical or palisade cells are also seen. With specific stains the granules, described below, tend to be more abundant at the base of the cell. The apex rarely reaches the lumen of the crypt. In tumors the cells not infrequently form glands and have been reported as discharging their secretion into the lumen. The majority of the cells in tumors are arranged in solid, closely packed masses surrounded by a definite fibrous stroma, while a small vessel is often seen entering the middle of the cell mass. Bailey has described elastic fibers in the stroma and thinks that this accounts for the characteristic contraction of the primary tumor. The nuclei are round and vesicular with a prominent nucleolus but may be oval, lobulated, or occasionally multinucleated. Mitochondria have been described by Kull at both ends of the cell. The Golgi apparatus is also doubled and Kull attributes to this apparatus at the base of the cell an endocrine function. The apparatus at the opposite end may be somewhat analogous to that in the thyroid cell. It may indicate either an excretory or secretory function or both.

The cytoplasm is finely vacuolated and shows the doubly refractile Maltese crosses characteristic of cholesterol, although a small amount of lecithin is also said to be present. Extraction of the metastatic tumor nodules in our second case yielded 19.98 mg. of cholesterol per gram. The lipid content of the cells
ARGENTAFFINE TUMORS

is probably responsible for the yellow color so frequently seen. In addition to
the vacuoles there are specific granules in the cytoplasm which are stained
with osmic acid, chrome salts, and silver. In this laboratory Dr. F. B. Mal-
lory has demonstrated that the granules also have an affinity for lead, which
can then be stained with hematoxylin. We may add, therefore, that the
granules are plumbiphilic. The only other cells which we have noticed show-
ing plumbiphilic granules similar to those in argentaffine tumors are the cells
in the adrenal medulla. These cells also reduce silver.

The argentaffinomas vary greatly in their ability to reduce silver. Masson
claims that they lose their affinity for specific stains after death and gain in
their affinity for acid, so that the later they are seen post mortem the more pink
and smooth will be the cytoplasm. We have found it difficult to get good
selective silver-stained preparations more than eight to ten hours after death.
In our experience Masson’s technic of silvering in block gave the best results,
although occasionally toning in the gold bath after the sections were cut was
necessary to blacken the granules further.

Significance of the Cells: Since cellular granules are usually associated with
cell function, it is readily understandable that most of the theories relating to
these cells deal with the granules. These have been regarded as artefacts,
secretory and non-secretory bodies, wandering leukocytes, chemoregulators,
absorbing cells, and both endocrine and exocrine glands. Macklin and
Macklin suggest that their distribution in the esophagus, stomach, etc., is
against an absorptive function. Toro believed that they absorbed acid or
base from the blood depending upon the pH of the gastro-intestinal contents.
Ciaccio, in 1906 and 1907, suggested their resemblance to the cells of the
adrenal medulla and thought that they might possibly form adrenalin. If
this were so, since one adrenal will hypertrophy in the absence of, or disease in,
the opposite adrenal, we reasoned that in cases of Addison’s disease there
should be a compensatory hypertrophy of the argentaffine cells in the gastro-
intestinal tract. Three cases of Addison’s disease in which suitable material
was available were studied and in no instance was there any increase in the
number of argentaffine cells.

Numerous feeding experiments have been attempted with marked vari-
ation in the results. Kultschitzky and others report an increase in the argent-
affin cells on feeding. Toro, on the other hand, claims that they are in-
creased on starvation. Erós and Kunos also report an increase on starvation
and on injection of hormones. Kull claims that neither starvation nor feeding
affects the number of cells. Feeding fat, protein and carbohydrate also show
similar differences in the results. Macklin and Macklin discuss the results of
feeding experiments.

Erós and Kunos claim to have produced a reticulocyte response in rats
with Bartonella anemia by injection of extracts of the gastro-intestinal tract of
pigs and chicks. The active principle they believe is contained in the argen-
taffine cells. The data set forth in their paper, however, are totally lacking in
evidence to support this conclusion.

Kahlau reports an increase in the argentaffine cells of the gastro-intestinal
tract in guinea-pigs after numerous small injections of insulin or of thyroid or
pituitary extract.
Masson suggests that the cells have a modified endocrine function, for which he uses the term "neurocrine." He thinks of them as similar to neuroepithelium and closely associated with the sympathetic nervous plexuses of the gastro-intestinal tract. While there is no definite proof of an endocrine function of these cells, there is some evidence in its support, namely, the double Golgi apparatus, the basal distribution of the granules and the fact that the cell borders rarely reach the lumen of the crypts. As to their origin, Masson thinks that they arise in the entoderm and form a diffuse placode after migrating from the intestinal mucosa. Simard and Van Campenhout, working in Masson's laboratory with grafts of chick intestine, showed that the argentaffine cells underwent budding and migration from the mucosa after 269 hours and that cell differentiation occurs in the absence of nervous elements. Schack also observed the migration of the argentaffine cells from the mucosa into the submucosa. He believes that there is a genetic relationship between the melanophores of the skin, adrenal cortical cells, and the argentaffine cells of the appendix.

Kull, on the basis of the fuxsinophile properties of the granular cells in the submucosa and mucosa, concluded that they were mesodermal in origin.

Raiford suggests an ectodermal origin. He believes that the cells have migrated early in life from the neural crest and have become adapted to a special function, forming part of the general chromaffine system. Other investigators also favor an ectodermal origin and point to the chrome reaction and the similarity of the extra-epithelial argentaffine cells to the paraganglionic elements. Lewis and Geschickter regard the argentaffine tumors as paragangliomas and hence subscribe to an ectodermal origin.

There is little doubt at present that the tumors arise from the Nicolas-Kultschitzky cells in the gastro-intestinal mucosa. The exact origin of the cells, however, is not at all clear. The evidence appears to be fairly well divided between the entodermal and ectodermal proponents. The function of the cells also remains a moot point.

We should like to submit a theory which separates the pathogenesis of tumor formation in the appendix from that in the remainder of the digestive tract. That the majority of argentaffine tumors show some invasion of adjacent structures is a well known fact. In the appendix tumor cells are found not only in the submucosa but also in the muscular layers and not infrequently in the serosa and mesentery. Masson has shown that many such tumors occurring in the tip of the appendix are the result of proliferating neuromata into which the argentaffine cells have grown. He also considers the possibility of these neuro-argentaffine tumors resulting from obliteration of the lumen by neuromata. Since, under these conditions, the mucous cells with an exocrine function can no longer discharge their secretory products, they atrophy and there are left behind only the argentaffine cells, which have an endocrine function. This is comparable to the persistence of islet cells following ligation of the pancreatic duct and atrophy of the acinar tissue.

In the material that we have studied it would appear that there may be two modes of origin of argentaffine tumors. In the appendix the lumen is usually obliterated, and while there may be numerous nerves, the number of argentaffine cells is quite small. We have also observed that not infrequently
argentaffine tumors occurring in non-obliterated appendices and elsewhere in
the gastro-intestinal tract show very little stroma. They are seen as small
submucosal masses of tumor cells sometimes not growing into the muscular
coats, and nerves are usually sparse or practically absent.

We have, therefore, on the one hand, a tumor composed of neuromatous
elements or schwannomata with few argentaffine cells, as in the obliterated
appendices, and on the other hand a tumor composed chiefly of argentaffine
cells and no nerves, usually seen outside the appendix. Is it not possible that
the submucosal tumors are true tumors while those in obliterated appendices
with an abundance of nerves represent an inflammatory process? Masson
suggests this latter mode of origin in his early investigations into the relation
of neuromata and argentaffine tumors. A further point in favor of this dif-
ferential type of argentaffine tumor formation is found in a survey of the litera-
ture, which shows that the number of cases with distant metastases is much
lower for appendiceal than for extra-appendiceal tumors, although the more
frequent early surgical removal of appendices may account for this difference.
The majority of malignant tumors occurring in the appendix showed only ex-
tension or metastasis to the regional lymph nodes.

SUMMARY

1. A series of 84 argentaffine tumors is reported. Three of these were ma-
lignant, arising in the small intestine.
2. Eighteen malignant argentaffine tumors not previously tabulated, have
been discovered in the literature, bringing the number to 64, excluding the 3
described here.
3. Argentaffinomas are encountered in from 0.2 per cent to 0.5 per cent of
appendices removed at operation.
4. The incidence of the small bowel tumors is less than one-half that of
carcinoids in the appendix. The former have a predilection for the terminal
ileum, tend to cause obstruction, and not infrequently metastasize.
5. All argentaffinomas are potentially malignant. Their grade of ma-
lignancy as a rule is low. Treatment is surgical.
6. The function of the argentaffine cell is not known; its origin is probably
from the entoderm.
7. It is suggested that argentaffinomas found in obliterated appendices may
be the result of proliferation of the argentaffine cells following chronic inflam-
mation, while the tumors of extra-appendiceal origin are true neoplasms.

REFERENCES

Note: For the most part references to be found in the papers by Raiford (36) and
Wyatt (46) are omitted here. The references marked with an asterisk (as *Bakke, R.)
are to malignant cases tabulated by Wyatt but not included in his bibliography.