The Endodermal Origin of Digestive and Respiratory Tract APUD Cells

Histopathologic Evidence and a Review of the Literature

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Twenty-seven small cell carcinomas of the lung and three tumors of the large intestine with combined adenocarcinomatous and small cell and/or anaplastic carcinoid-type histologic features were studied by light and electron microscopy. It was shown that the small cells have morphologic characteristics of APUD cells. Also presented are the histologic features of a carcinoma of the lung with large cell undifferentiated carcinoma, adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma areas in the primary site and in several metastatic foci. Two of the renal metastases showed small cell carcinoma. The combined tumors and the numerous other similar neoplasms described in the literature and reviewed here suggest an endodermal origin for digestive and respiratory tract APUD cells based on the hypothesis that cancer is a clonal proliferation, and mucous and squamous cell differentiation is an endodermal rather than neural crest characteristic. The ultrastructural features of tumors of cells of known neural crest origin, including a medullary carcinoma of the thyroid, three carotid body tumors, a pheochromocytoma, and two cutaneous melanomas were compared with those of other APUD cell tumors including small cell carcinomas of the lung, two bronchial carcinoids, a carcinoid of the appendix, and a carcinoid of the kidney. Cells of the latter group sometimes possessed cytoplasmic tonofibrils, round compact masses of cytoplasmic microfilaments, and ductal lumina. These features were lacking in the former group and may signify a different embryologic origin. The histologic, histopathologic, and embryologic evidence regarding the origin of digestive and respiratory tract APUD cells is reviewed, showing that the former are, and the latter probably are, of endodermal and not neuroectodermal origin. (Am J Pathol 96:5–20, 1979)

THE APUD SYSTEM, based on the common property of some cells to concentrate and decarboxylate amine precursors, was proposed by Pearse [1] to encompass adrenal chromaffin cells, enterochromaffin cells, mast cells, pancreatic B cells, pituitary corticotrophs and melanotrophs, and thyroid C cells, Since then, many more cell types have been incorporated in it. In 1969, Pearse [2] suggested that cells belonging to the APUD system may have a common embryologic origin in the neural crest. Subsequently, using formaldehyde-induced fluorescence after L-dopa administration, Pearse and Polak [3] demonstrated in mouse embryos that fluorescent cells can be seen in temporal sequence in the mesenchyme of

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the pharynx, the fourth pharyngeal pouch, the gastric and duodenal primordia, the presumptive dorsal pancreas, and the epithelium of the stomach, duodenum, and pancreatic ducts. Similar changes were observed in the trachea and bronchi. A migration of neural crest cells into the gastrointestinal and respiratory epithelia, and perhaps the pancreatic ducts, was inferred. An alternative explanation is that the migrating cells were neuroblastic precursors of the intramural autonomic ganglion cells, and the intraepithelial APUD cells developed from endodermal precursor cells concurrently with the neuroblastic migration. Later, using a similar technique along with cytochemistry and electron microscopy, Pearse and co-workers [4] came to the conclusion that some pancreatic islet cells are derived from the neural crest, whereas others may be endodermal.

While studying small cell carcinomas of the digestive and respiratory tract, the author has come across several examples of tumors that appear to be composed of cells morphologically resembling APUD cells in addition to cells with mucous or squamous differentiation. Numerous examples of tumors with a similar but less anaplastic APUD component in combination with mucin secretion or a mucinous adenocarcinoma have been reported to occur in the digestive tract. This evidence suggests that the APUD cells of the digestive and respiratory tracts may arise from the same precursor cell as the other epithelial cells. To further explore this assumption, examples of tumors composed of APUD cells of accepted neural crest or neuroectodermal origin,[5] such as medullary carcinoma of the thyroid,[6,7] carotid body tumor,[8] pheochromocytoma,[9,10] and melanoma,[10,11] were examined ultrastructurally and contrasted with examples of endocrine tumors of the respiratory and digestive tracts along with a carcinoid of the kidney to see if any consistent morphologic differences occurred reflecting different embryologic origins. This paper presents the results of this study and observations on the small cell carcinomas. Additionally, published pathologic, histologic, and embryologic evidence concerning the origin of digestive tract endocrine cells is reviewed. Due to the sparsity of APUD cells in the respiratory tract, similar studies regarding their origin have not as yet been undertaken.

Materials and Methods

Material for the small cell carcinoma study comprised biopsies of 27 small cell carcinomas of the lung, three surgically resected carcinomas of the large intestine that also showed areas of small cell or anaplastic carcinoid-type differentiation, and histologic sections from an autopsy performed on a 62-year-old man with a carcinoma of the lung. Tissues from the autopsy were examined by light microscopy only, whereas the other tissues were studied by both light and electron microscopy.

In the study comparing tumors with APUD features of known neural crest origin with other tumors having APUD characteristics, light and ultrastructural examination was

performed on two bronchial carcinoids, a carcinoid of the appendix, a carcinoid of the kidney, a medullary carcinoma of the thyroid, three carotid body tumors, a pheochromocytoma of the adrenal gland, and two melanomas of the skin.

For light microscopic examination, in addition to the routine stains, the following stains were performed on sections of all tumors other than the small cell carcinomas of the lung: Alcian blue, pH 2.5-PAS to detect epithelial mucin, a Masson-Fontana stain for argentaffin granules, and a Grimelius stain for argyrophil granules.

Results

Small Cell Carcinoma of the Lung

APUD-type dense core granules (Figure 1) were found in seven (26%) of the pulmonary small cell carcinomas. They were generally scanty, but in three tumors were present in almost every cell. Cytoplasmic microtubules were seen in many cells (Figure 2). Desmosomal junctions were present in five tumors. In these and three other tumors, cytoplasmic microfilament bundles were present (Figure 2). Tripartite junctional complexes with suggestive lumen formation were seen in two instances, both in mediastinal lymph node metastases (Figure 3).

Lung Carcinoma With Mixed Differentiation

A large tumor was present in the left mainstem bronchus. Histologically, it was an undifferentiated carcinoma composed of large, polygonal cells (Figure 4). Foci of glandular differentiation with mucin secretion (Figure 5), squamous differentiation (Figure 6), and giant cell change were present. Metastatic tumor was found in several organs. It was of the large cell, undifferentiated variety except for two of the metastatic foci in the kidney that had the appearance of small cell carcinoma (Figure 7).

Carcinomas of the Large Intestine

These were located in the cecum, transverse colon, and rectum, respectively. All three were fungating, ulcerated masses that were partly composed of banal, mucin-secreting adenocarcinoma (Figure 8). The cecal tumor had, in addition, large areas composed of small, oval cells with dark nuclei and scanty cytoplasm suggestive of small cell carcinoma. These cells lacked mucin but, in many places, formed rosettes (Figure 9) and contained cytoplasmic, argyrophilic granules (Figure 10). Ultrastructural examination demonstrated that these granules were similar to granules of APUD cells (Figure 11). Both the endocrine and adenocarcinomatous patterns were present in regional lymph node metastases.

Areas of small cell carcinoma were present in the submucosal portion of the tumor in the transverse colon (Figure 12) in addition to adenocarcinoma (Figure 13). The tumor infiltrate in the muscularis propria and

serosa and metastatic nodules in the liver and regional lymph nodes were exclusively of the small cell variety. Radiologic and bronchoscopic examination failed to demonstrate a primary tumor in the lung. Argyrophil and argentaffin stains were negative and no APUD-type granules were found on ultrastructural examination. The patient died a few months after colonic resection. No autopsy was performed.

The rectal tumor penetrated the full thickness of the bowel wall, but no metastatic tumor was found. In addition to well-differentiated adenocarcinoma, two other histologic patterns were present in the deeper portions of the tumor. One was a colloid carcinoma-like area with signet-ring cells, strongly positive with alcian blue, floating in lakes of mucin (Figure 14). Some of these cells contained argyrophil granules, but the samples taken for electron microscopy demonstrated only mucin droplets in the cytoplasm. The other pattern was a microglandular, rosette-like arrangement of cells that lacked mucin but contained cytoplasmic, argyrophilic granules (Figures 15 and 16). Ultrastructurally, the cytoplasm contained numerous, membrane-bound, 200–300 nm diameter, secretory granules with homogeneous content of variable electron density (Figure 17). Cells containing both mucin droplets and dense-core neurosecretory type granules were not identified in any of the intestinal tumors.

APUD Tumors of Known Neural Crest Origin and Other APUD Tumors

A common feature of all the tumors in this group was the presence of intercellular junctions that were generally poorly developed desmosomes. Junctional complexes were seen occasionally in the nonneural crest group, but definite lumens were associated with these only in the rosette-forming areas of the cecal and rectal tumors, and suggestive lumens in two of the small cell carcinomas of the lung described above. Cytoplasmic microfilaments were present in all cases, often in small, loose bundles, and microtubules were seen occasionally. Dense aggregates of filaments resembling tonofibrils were seen only in the carcinoid of the kidney (Figure 18) and in a small cell carcinoma of the lung. Additionally, the renal and appendiceal carcinoids contained large, round, cytoplasmic inclusions that indented the nucleus and were visible on light microscopy. They consisted ultrastructurally of large masses of microfilaments that occupied all except the peripheral portion of the cytoplasm. Scattered organelles were entrapped within them (Figure 19).

Discussion

The observations on small cell carcinomas show that cytoplasmic granules similar to those seen in APUD cells are frequently present. This is also

the experience of others.[12] Functionally, small cell carcinomas are known to sometimes produce polypeptide hormones or amines that are normally produced by cells of the APUD system.[5,13] Light microscopic and/or ultrastructurally demonstrable small cell characteristics can hence be reasonably considered to be an index of APUD cell differentiation. The APUD nature of carcinoid tumors is accepted, and it is believed that small cell carcinomas may be merely a highly malignant variant of these neoplasms.[13]

One of the features of respiratory and digestive tract epithelial cells is their ability to produce acidic and/or neutral mucoproteins. In primary tumors of these regions, this can be used as a marker of endodermal origin. If APUD-type cells are present in these neoplasms, it suggests that they are of endodermal origin too, provided it can be shown that they are neoplastic and not just innocent bystanders that have been trapped in the tumor, or a reactive hyperplasia incited by the presence of the tumor. The occurrence of the APUD-type cells in metastatic foci of the tumor or in locations well beyond the normal confines of the mucosa provides such proof. This type of evidence is present in the autopsy study of the lung carcinoma and in all three of the intestinal carcinomas.

Examples of similar tumors observed by other authors are listed in Table 1. The frequency of admixture of APUD and endodermal cell derivatives in tumors of the digestive tract argues against a fortuitous coexistence of neoplastic transformation in the same site of cells of disparate embryologic origin. The evidence for the respiratory tract is similar but scanty.

Assuming that all cells with the histochemical, hormonal, and ultrastructural characteristics subsumed by the acronym APUD are derived from the neural crest, Pearse [2] proposed that the endocrine cells of the

Table 1—Tumors Containing Both APUD and Endodermal Cell Derivatives

Mucinous carcinoids of appendix,[14,15,16,17,18,19] intestines,[20,21] and bronchus.[13]
Mucinous carcinoid of appendix with Paneth cells.[22]
Composite adenocarcinomas and carcinoids of stomach,[23,24] intestines,[20,25,26,27] and gall bladder.[28]
Composite oat cell carcinomas and adenocarcinomas of stomach.[29]
Pancreatic adenocarcinoma with islet cell features.[21,30,44]
Argentaffin/argyrophil cell proliferation in gastric[31,32] and colonic adenomas.[33,34]
Argentaffin/argyrophil cells in adenocarcinomas of stomach,[24,31,35,36,37,38] large intestine,[33,34,38,39] and appendix.[40,41]
Carcinoid syndrome in adenocarcinomas (argentaffinomas) of stomach.[24,35,38]
ACTH production in adenocarcinoma of colon.[42]
ADH production and inappropriate ADH-secretion syndrome in adenocarcinoma of pancreas.[43]
Endocrine, mucous, and squamous cells in a pituitary tumor.[45]

digestive tract originate from the neural crest and not the endoderm as previously believed. Embryologic experimental data, however, favor endodermal origin. Due to the sparsity of APUD cells in the respiratory tract, experimental data for their embryologic origin do not exist and the evidence for their endodermal origin is purely circumstantial.

In 1932, Simard and Van Campenhout [46] grafted non-innervated chick embryo intestine before the onset of migration of neural crest cells into chick chorioallantoic membrane and showed that the intestinal argentaffin cells developed normally. More recently, Andrew,[47] using chorioallantoic transplants of chick blastoderm from which neural crest had been excised, showed that gastrointestinal enterochromaffin cells are not of neural crest origin. By grafting the neural tube and crest tissue of embryonic quail into chick embryos from whom corresponding areas had been excised, Le Douarin and Teillet [48] came to a similar conclusion. In both these experiments, it was also shown that the neural cells migrating into the gastrointestinal tract gave rise to the intramural autonomic ganglia, in effect explaining the destiny of the migrating fluorescent cells observed by Pearse and Polak.

In a slightly different approach to the problem, Andrew [49] grafted presumptive gut into chorioallantoic membrane before and after the time of arrival of neural crest cells. It was shown that the progenitors of enterochromaffin cells are present in presumptive gut before prospective neuroblasts arrive. It was also shown that the presence of these neuroblasts in the gut is not necessary for the developement of enterochromaffin cells.

Neoformation of insulin-producing islets from the exocrine pancreatic ductules by budding and transformation of ductal cells into B cells has been demonstrated following ligation of the pancreatic duct in rats.[50] After destruction of B cells by alloxan, regeneration appears to occur from non-granulated, clear cell precursors that are normally present in islets and ductules.[51] In a morphologic study of the embryogenesis of human pancreatic islets using light and electron microscopy, Like and Orci [52] showed that A, B, and D islet cells appeared to arise from ductal cells. None of the above observations, however, rules out the possibility that cells of neural crest origin had populated the ducts and ductules prior to islet formation.

The embryologic origin of pancreatic B cells in rats was studied by Phelps [53] and Pictet et al.[54] They removed the ectoderm before neural tube or neural crest formation in rat embryos and observed the development of the pancreas from the mesoendoderm in tissue culture. B cells of the islets were shown to develop independent of the neural crest. Andrew [55] used neural crest grafts employing either the quail nuclear marker

or ^{3}H-thymidine labeling (of quail or chick grafts) to show that the pancreatic A, B, and D cells are of non-neural crest origin.

In all the foregoing embryologic experiments, it is conceivable that digestive tract APUD cells arose by migration of ectodermal precursor cells before neural tube or neural crest formation. Pearse [56] now views these APUD cells as arising from neurally programmed cells of the ectoblast. It has been shown recently by Fontaine and Le Douarin,[57] using the quail-chick chimera, that the hypoblast participates only in the formation of the extraembryonic endoderm, the embryonic endoderm being produced by migration of cells of the epiblast through the primitive streak. However, they also demonstrated that migration of cells from the ectoderm to the endoderm ceases before the formation of the neural crest or the early neural ectoderm. They state that "cells of the early neural ectoderm do not contribute to endoderm formation before the stage at which the neural crest is individualized." Since the area of the epiblast from which the cells migrate into the hypoblast is linked to the area from which the neural plate later develops, Pearse [56] speculates that the migrating cells may be neurally programmed. But the experiment demonstrates that these cells do not merely migrate *into* the embryonic endoderm but *constitute* it. In addition, the following evidence nullifies the proposition that the gastrointestinal APUD cells have an origin in precursor cells that are distinct from those giving rise to the other cellular elements of the endodermal epithelium.

In the experiment of Pictet et al,[54] pancreases formed in only 25% of the cultures. However, a significant feature was that islet or exocrine tissue never developed alone in the absence of the other component, suggesting that they have a common origin. Since the exocrine pancreas is certainly an endodermal derivative, the islets too are most likely of similar origin.

Cheng and Leblond [58,59] have used ^{3}H-thymidine labeling to show that all the cells of the small intestinal epithelium of mouse, including the enteroendocrine cells, develop from a common undifferentiated precursor, the crypt-base columnar cell. The enteroendocrine cells, mucous cells, and columnar cells have approximately the same turnover time. They migrate towards the villus tip as they mature and are extruded from the surface. It was also found that enteroendocrine cells with recognizable secretory granules do not divide, confirming an earlier observation of lack of mitotic figures in these cells.[33]

Autoradiographic studies employing ^{3}H-thymidine labeling [60,61] of mouse colon cells have shown that here again a common precursor cell, the vacuolated cell of the lower two-thirds of the crypt, gives rise to the mucous, columnar, and argentaffin cells of the mucosal epithelium.

A slightly different approach has been used to find the stem cell of

gastric epithelium. Matsuyama and Suzuki [62] grafted portions of the fundic segment of the stomach of newborn mice into the subcutaneous tissue of the abdomen. Initially, after a period of necrosis, the viable epithelium was represented by a single layer of regenerated, immature mucous cells. No other cell types were present. By one month, the mucosa had fully regenerated and contained the normal complement of parietal, chief, and argyrophil cells. This evidence suggests that immature mucous cells (neck mucous cells) are the precursors of gastric argyrophil cells.

Table 2 lists evidence of the existence of cells that are morphologic hybrids, having both endodermal and APUD cell characteristics. Also included is a human carcinoid of the colon whose cells were shown to grow as mucin-producing, signet-ring cells on xenogeneic transplantation into hamster cheek pouches.[65] An initial passage in millipore chambers in rats had shown that only carcinoid cells were being transplanted.

Another approach to the problem is to observe the potential for differentiation in tumor cells. This method also has the capability of excluding nonneural, ectodermal origin. The assumption in interpreting these "natural experiments" is that tumors are composed of a multiplying population of dedifferentiated cells, some of whose progeny differentiate into more mature, recognizable cell types whereas others remain in the dividing, dedifferentiated, precursor pool. It is highly unlikely that two or more separate precursor cells with completely independent maturation potentialities will be present simultaneously in the same neoplasm. It is generally accepted that cancer is a clonal proliferation.[66,67] In tissue cultures of breast carcinoma, for example, it was observed that two morphologically distinct populations may be present in the same culture.[68] Subculturing after meticulous separation of each cell type, however, invariably resulted in growths composed of combinations of the two cell populations as in the primary cultures, suggesting that the dividing cell pool was monoclonal. In a neoplasm demonstrating more than one type of cellular differentiation, if the embryologic source of one of the maturation variables is known, it can be assumed that the source of all the other variables is the same. In this context, the mixed APUD and endodermal

Table 2—Evidence of Existence of Morphologic Hybrid Cells

Composite acinar-islet and ductal-islet cells in normal pancreas of rat, guinea pig, chicken, frog, goat, and rhesus monkey.[63,64]
Neurosecretory granules and mucin within same cells in human and experimental rat and mouse gastric adenocarcinomas,[24] mouse small intestine[58] and normal human gastric mucosa.[24]
Growth of human colonic carcinoid as mucinous, signet-ring cells in hamster cheek pouches.[65]

cell tumors presented here and the tumors referred to in Table 1 are evidence corroborating the histologic evidence regarding the stem cells of the gastrointestinal mucosa presented above.

The limited study of the morphologic characteristics of tumors of cells of known neural crest origin described in this paper did not reveal any major differences from those seen in the nonneural crest group of APUD tumors. However, the presence of large, rounded masses of cytoplasmic microfibrils described in some examples of the second group was not observed in the first. These masses have been reported in a bronchial carcinoid [69] and in pituitary adenomas.[70] Tonofibrils were also seen exclusively in the second group. They have been described in an islet cell carcinoma of the pancreas [71] and in pituitary endocrine tumors.[45] Ductal lumina were seen in two small cell carcinomas of the lung and the rosette-forming areas of the cecal and rectal tumors but not in any others.

A review of the literature shows that tonofibrils, microfilament masses, and ductal lumens have not been described in neoplasms of the known neural crest group.[72-78] Furthermore, the APUD cells of the normal lung [79] and gastrointestinal tract [46] have apices that reach the lumen and bear surface microvilli. Tripartite junctional complexes incorporating a tight junction connect the luminal ends of these cells with neighboring cells. These features are lacking in thyroid C cells,[80,81] carotid body cells,[82] adrenal chromaffin cells,[82] and melanocytes.[82] However, there is no denying the fact that the component cells of the APUD system display remarkable functional and morphologic similarities. What could be the possible explanation for this uniformity? Andrew [5] comments that "parallel evolution can result in similar characteristics in unrelated forms." Perhaps, as Pearse [2] suggested but discounted in favor of the neural crest theory of origin, "the various APUD cells may be of diverse origin but have developed a similar set of biochemical mechanisms in response to similar specific stimuli, at present of unknown nature."

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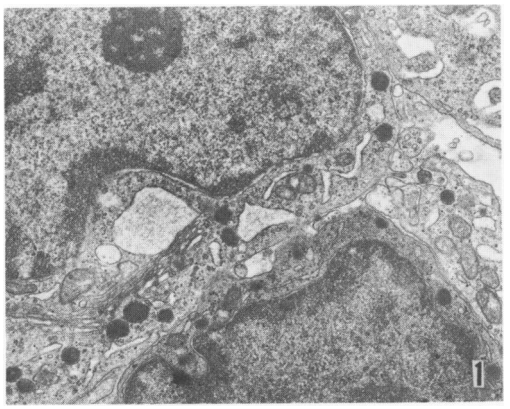
Figure 1—Small cell carcinoma of lung, with many APUD-type cytoplasmic granules. (× 9000)

Figure 2—Small cell carcinoma of lung. Two tumor cells are seen, one with microtubules and the other with a bundle of microfilaments. (× 24,000)

Figure 3—Small cell carcinoma of lung, metastatic in a mediastinal lymph node. Junctional complexes converging toward an ill-formed lumen (*L*) are seen. (× 13,200)

Figures 4-7—Carcinoma of lung. **Figure 4**—Large cell undifferentiated area. **Figure 5**—Adenocarcinomatous area. Mucin (*arrow*). **Figure 6**—Squamous cell area. **Figure 7**—Metastatic focus in kidney, showing small cell carcinoma. (**4,** H&E, × 400; **5,** PAS, × 290; **6,** H&E, × 290; **7,** H&E, × 400)

Figures 8-11—Cecal tumor. **Figure 8**—Well-differentiated adenocarcinoma. **Figure 9**—Small cell carcinoma with rosette formation. **Figure 10**—Similar area with cytoplasmic, argyrophilic granules (*arrow*). **Figure 11**—Electron micrograph of deparaffinized tissue from small cell area, showing APUD-type cytoplasmic granules. (**8,** H&E, × 76; **9,** H&E, × 290; **10,** Grimelius, × 1350; **11,** × 15,000)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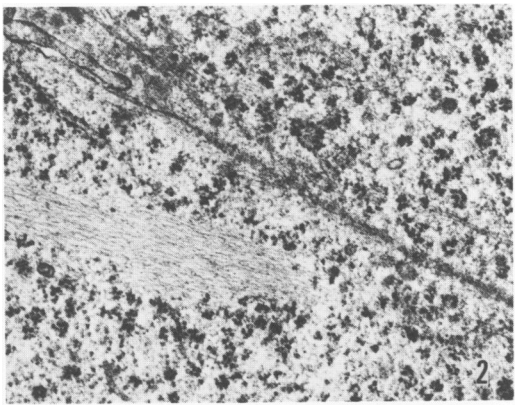
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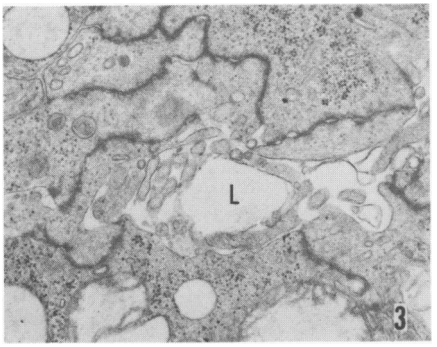
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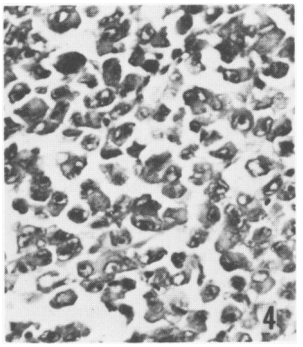
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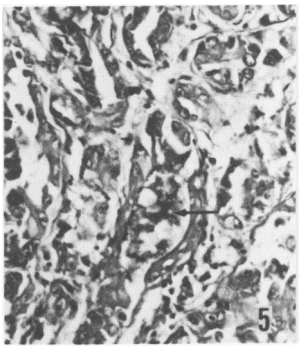
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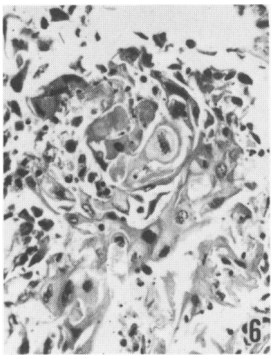
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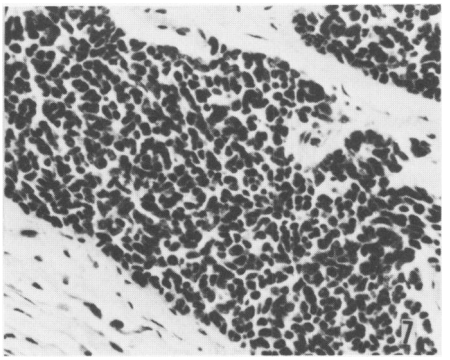
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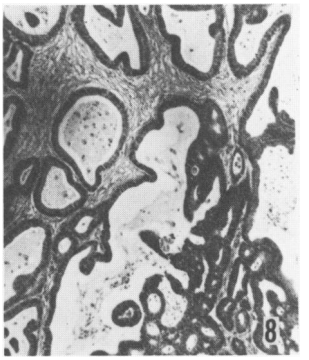
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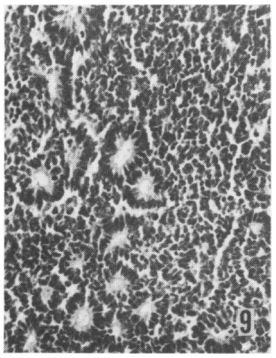
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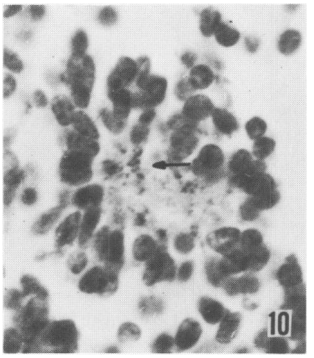
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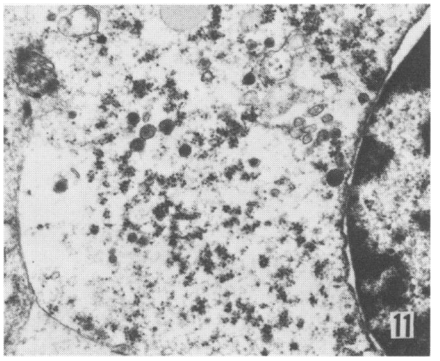
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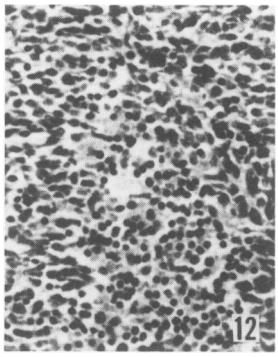

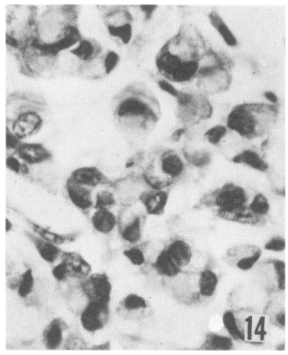

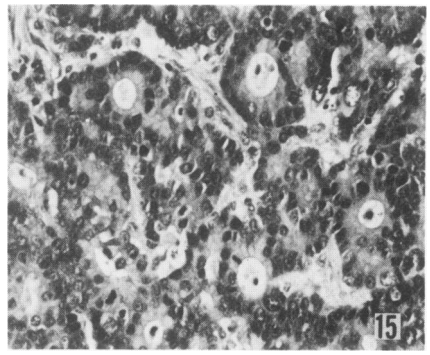

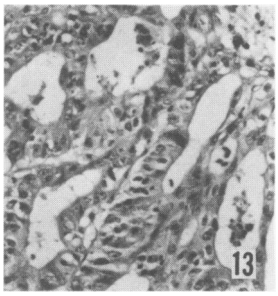

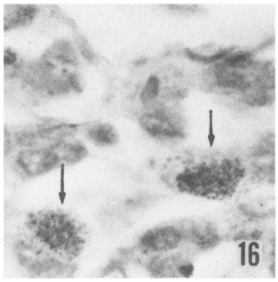

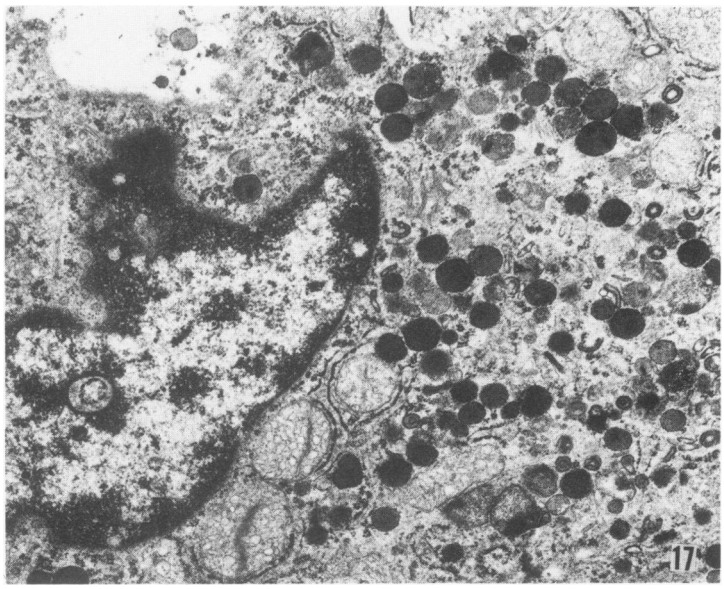

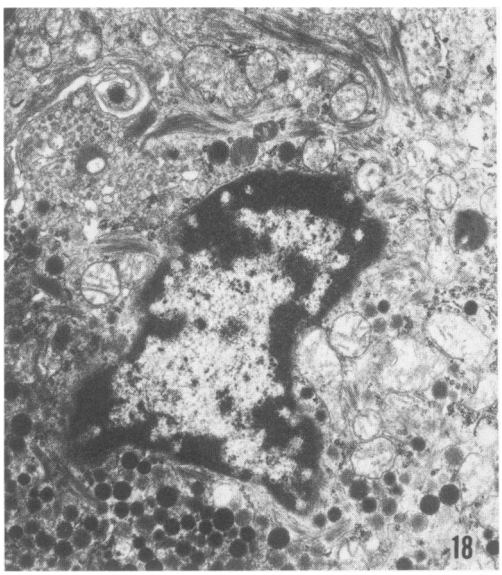

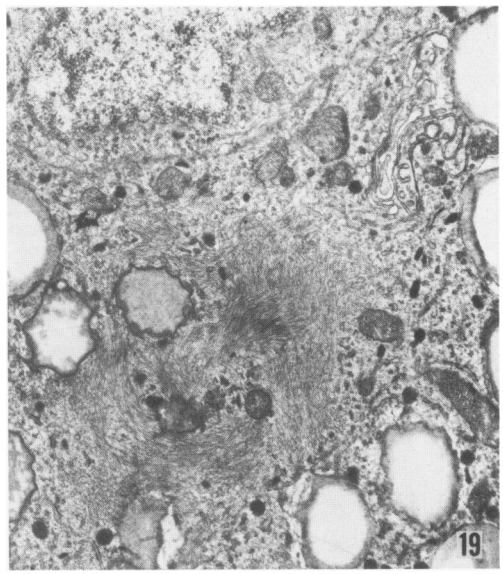

Figures 12 and 13—Transverse colon tumor. **Figure 12**—Small cell carcinoma area. **Figure 13**—Adenocarcinomatous area. (H&E, × 320). **Figures 14 through 17**—Rectal tumor. **Figure 14**—Colloid carcinoma. **Figure 15**—Area with ductal structures and rosettes. **Figure 16**—Cytoplasmic argyrophilic granules (*arrows*) in an area similar to that in Figure 15. Grimelius stain. **Figure 17**—Tumor cell showing APUD-type secretory granules with tight membranes and content of variable density. (**14,** H&E, × 800; **15,** H&E, × 336; **16,** Grimelius, × 1150; **17,** × 13,200) **Figure 18**—Carcinoid of kidney. Cell shows cytoplasmic, APUD-type secretory granules and dense tonofilament bundles (tonofibrils). (× 8750) **Figure 19**—Carcinoid of the vermiform appendix. Large, compact mass of cytoplasmic microfilaments with entrapped mitochondria, secretory granules, and lipid droplets is seen. (× 8750)