Virchows Arch. A Path. Anat. and Histol. 366, 257—274 (1975)

Argyrophil Cell Carcinomas (Apudomas) of the Uterine Cervix

Light and Electron Microscopic Observations of 5 Cases*

Ryuhei Tateishi, Akira Wada, Kenichi Hayakawa, Jiro Hongo, Seiji Ishii, and Naoki Terakawa

Departments of Pathology and Gynecology, The Center for Adult Diseases, Osaka, Japan

Received December 23, 1974

Summary. Of a series of 97 invasive carcinomas of the cervix, 5 were found to have argyrophil tumor cells, and 3 of these 5 tumors were studied by electron microscopy. The ages of the 5 patients ranged from 36 to 49 years, with a mean age of 42.4 years. The morphologic features of these five tumors were well consistent with those described on a variety of endocrine polypeptide neoplasms such as thyroid medullary carcinomas, carcinoids, pancreatic islet-cell tumors, and oat cell carcinomas of the lung.

Microscopically, the 5 tumors were characterized by the formation of solid-sheets, ribbons, streams, and rosettes. They were characterized electron microscopically by the presence of neurosecretory-type granules, the abundance of intracytoplasmic microfilaments, the absence of tonofibrils, and the paucity of desmosomal attachments. On the basis of the microscopic, electron microscopic and cytochemical characteristics, it is suggested that the tumors are a specific type of cervical carcinoma derived from the argyrophil cells, normally found among the linings of the endocervical glands and the cervical squamous epithelium. We believe these 5 tumors should be regarded as an endocrine tumor, another member of apudomas.

Key words: Carcinoma of the Cervix — Argyrophil Cell Carcinoma — Argyrophil Cells — Apudomas.

In a long series of papers, Pearse and co-workers (Pearse, 1966, 1968, 1969; Pearse *et al.*, 1972b) introduced the concept of the APUD series to characterize a variety of polypeptide hormone-secreting cells sharing a number of ultrastructural and cytochemical characteristics, including the most constant feature, the ability to take up and decarboxylate amino acid precursors of fluogenic amines. The initial letters APUD are derived from their fluorogenic properties (Amine and Amine Precursor Uptake and Decarboxylation). At the present time, 20 different polypeptide hormone-secreting cells are listed as members of the APUD series, widely distributed in endocrine organs and in non endocrine organs such as the skin, the gastrointestinal tracts, the respiratory tracts, and the urogenital tracts.

The term "apudomas" was coined by Sziji *et al.* (1969) to link together a variety of endocrine polypeptide tumors that arose from the cells of the APUD series, including thyroid medullary carcinomas, carcinoids in different organs, pancreatic islet-cell tumors, melanomas, and pheochromocytomas. Although apudomas have been found frequently in the thyroid glands, the gastrointestinal tracts, and the respiratory tracts, only rarely has been reported such a lesion originating in the urinary bladder or in the uterine cervix (Feyrter, 1951). We

* Presented at the 11th international cancer congress, Florence, Italy, October 24, 1974.

have found in the literature only one case of carcinoid in the uterine cervix (Abdores-Saavedra *et al.*, 1972) that was concerned with its possible origin from the argyrophil cells in the cervix (Fox *et al.*, 1964).

In the present study, based on 97 uteri with an invasive cervical carcinoma, we have encountered 5 examples that showed tumor cells containing argyrophil granules. Of the 5 tumors, 3 were studied by electron microscopy. These 5 tumors showed the histological, and ultrastructural features common to apudomas in different organs. The purpose of this paper is to describe the light and electron microscopic features of the 5 tumors.

Material and Methods

During a period of approximately 2 years (from July, 1972 to August, 1974) a total of 97 uteri with invasive cervical carcinomas were resected at The Center for Adult Diseases, Osaka. Of the 97 tumors, 82 were in clinical Stage I, and the remaining 15 in Stage II. In all cases, the cervices were serially sectioned, and usually we obtained 8 blocks from each cervix. Formalin-fixed and paraffin-embedded sections from each block were stained with hematoxylin and eosin, and were impregnated with Grimelius nitrate-silver (1968).

Among the 97 tumors, 5 were found to have argyrophil tumor cells, while the remaining 92 contained no argyrophil cells within the tumors. These 5 tumors found to contain the argyrophil tumor cells were submitted to further studies. Additional sections were prepared from the 5 tumors and were processed by Periodic acid-Shiff (PAS), Gomori's silver impregnation for reticulum fibers, Fontana-Masson argentaffin method (Pearse, 1972a), and alkaline Congo red method (Puchtler *et al.*, 1962).

For electron microscopy, the fresh tumor tissues (Cases 1, 2, and 3) obtained at biopsy were fixed in cold cacodylate-buffered, 2.5% glutaraldehyde, pH 7.4, for one hour, post-fixed in buffered, 1% osmium tetroxide, pH 7.4, for another one hour, dehydrated in graded ethanols, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead nitrate.

Results

The clinical and gross pathological informations on the 5 patients were summarized in Table 1.

Light Microscopic Findings. The tumor cells varied considerably in both shape and size in different tumors and within areas of the same tumor.

Typical tumor cells showed small-round or oat-shaped, hyperchromatic nuclei with faintly eosinophilic, scanty cytoplasm (Figs. 1 and 2). A second cell type was of polyhedral shape with a more prominent cytoplasm that varied in staining characteristics from basophilic to acidophilic (Figs. 3 and 4). The nuclei were slightly larger, less hyperchromatic, and round or oval in shape. Either of the cell types was dominant in a given tumor. In Cases 1 and 2, the tumors were composed predominantly of small cells, while in the tumor of Case 5 polyhedral cells were predominant. Mitotic figures were common, and were more frequently observed in association with the small cell type.

The pattern of growth also varied from tumor to tumor, and within the same tumor. Basically, the tumors were highly cellular, and were composed of solid-sheets of neoplastic cells with delicate vascular septa that divided the sheets into irregular cell nests (Figs. 1–3). In some areas of Case 1, 2 and 3, the cell nests composed predominantly of small, spindle-shaped cells showed a streaming pattern reminiscent of oat cell carcinoma of the lung (Fig. 2).

Table 1. Summary of clinical history and gross pathologic findings of the 5 cases

Case No.	Age at diagnosis	Clinical history	Clinical stage	Gross appearance
1	36	Gravida 8, Para 2 Intermittent vaginal bleeding, 70 days	IIA	Polypoid tumor, 3 cm in diameter, extending from the posterior lip into the vagina with submucosal involvement of posterior vaginal wall
2	36	Gravida 2, Para 2 Contact bleeding, 120 days	IB	Nodular tumor, 1 cm in diameter, in the connective tissue of left lateral aspect of the cervix, with a flat surface ulcer
3	46	Gravida 1, Para 1 Intermittent vaginal bleeding, 180 days	IB	Large tumor nodule encircling the cervical canal with a flat ulcer surrounding most of the external os. Regional lymph nodes were involved
4	49	Gravida 2, Para 0, Menopause, age 45. Intermittent vaginal bleeding, 75 days	IB	Nodular tumor, 2 cm in diameter in the cervical connective tissue with a slightly excavated surface at the right posterolateral aspect of the os
5	45	Gravida 3, Para 2, Supravaginal hysterectomy 18 yrs. prior to diagnosis. Intermittent vaginal bleeding, 7 days	IB	Polypoid tumor, 1 cm in diameter, growing out from the posterior wall of the cervical canal with nodular invasion into the connective tissue

A second pattern of growth occurring in 4 tumors was the formation of intercellular spaces (Figs. 3 and 4). Tiny, ill-defined intercellular spaces, usually filled with PAS-positive material, were scattered within the cell nests. PAS staining unmasked underlaying, tiny spaces when they were indistinct on hematoxylin and eosin stained sections. Well-defined intercellular spaces such as rosettes or gland-like lumens were found in 2 tumors (Figs. 4 and 5). When the cells arranged around a small-round or an oval lumen were not surrounded by a supporting stroma, the patterns were here defined as "rosettes" or "gland-like lumens" respectively. The cells forming the rosettes or gland-like lumens were usually prismatic or columnar in shape. Brightly eosinophilic cuticles were often seen in the apical borders of the cells forming the lumens. A small amount of PAS-positive material was occasionally accumulated in the lumens (Figs. 4 and 5).

Arrangement of tumor cells in ribbons or trabeculae occurred in 2 tumors. True glandular differentiation of tumor cells was present in 2 tumors; these glands were usually empty. Two tumors contained areas of squamous metaplasia which occurred only in the center of the cell nests.

The stroma of the tumors usually consisted of a rather delicate, fibrovascular connective tissue. In areas of Case 5, broad, hyalinized septa divided the masses of tumor cells into nests of varying sizes, presenting a pattern resembling that of

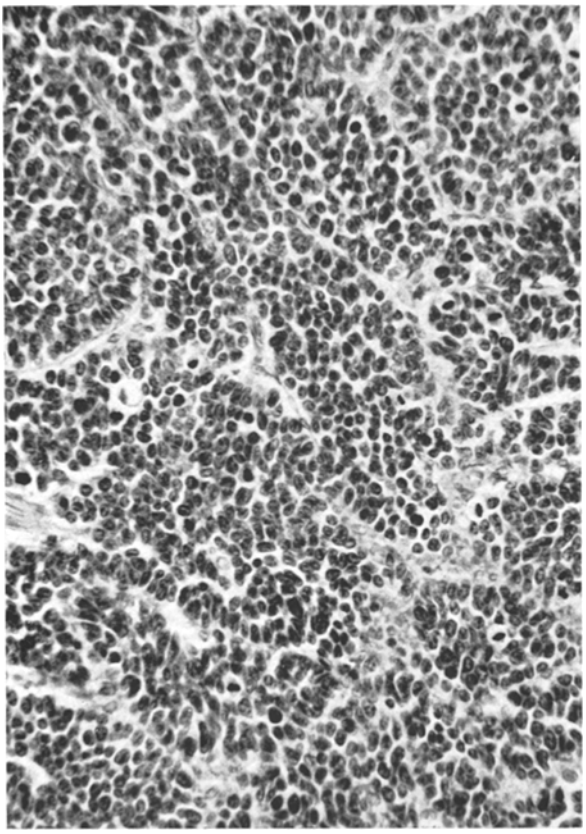


Fig. 1. Case 1. Solid nests composed predominantly of small-round cells with fine fir-tree stroma. Numerous mitotic figures are present (H and E, ×700)

thyroid medullary carcinomas (Fig. 6). The hyalinized septa were negative for alkaline Congo red reaction applied for the detection of amyloid.

The argyrophil method of Grimelius revealed the presence of tumor cells containing argyrophilic granules. These argyrophilic tumor cells varied widely in frequency in different tumors, and within different areas of even the same blocks of a given tumor. Tumors of Cases 1, 2 and 5 contained a moderate number of the argyrophilic tumor cells, diffusely scattered within the tumors, while the other 2 tumors contained far smaller numbers of the argyrophilic tumor cells, being located in small areas of the tumors. The argyrophilic tumor cells were oval, triangular or spindle-shaped, and often extended long cytoplasmic processes among other tumor cells (Figs. 7 and 8). No tumor cells containing argentaffin granules were present within the 5 tumors.

Grimelius method also disclosed the presence of argyrophilic cells in the normal cervical mucosa. Of 54 cervices in which adequate sections were available 19 contained the argyrophilic cells among the lining of either the endocervical glands (6 cases), or the cervical squamous epithelium (8 cases), or of both sites

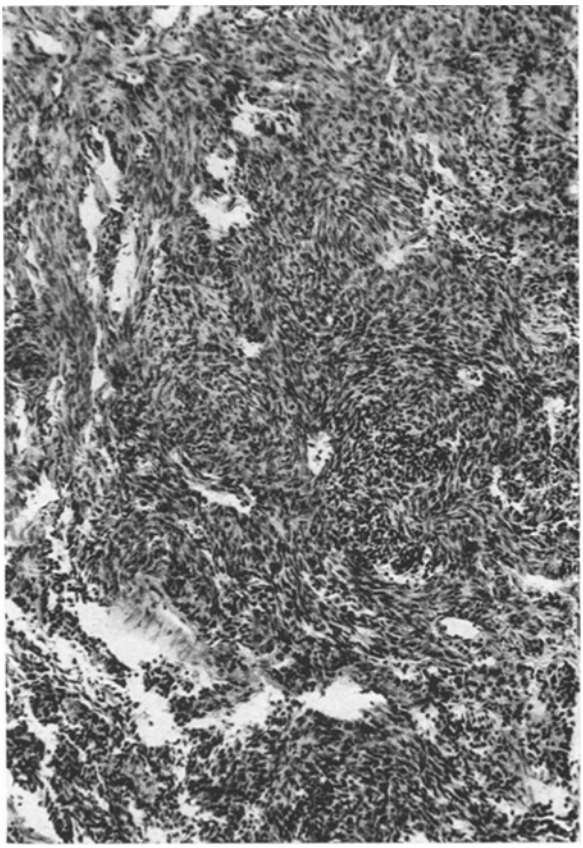


Fig. 2. Case 2. Tumor cell nests composed predominantly of small, spindle-shaped cells show streaming patterns (H and E, ×400)

(5 cases). These argyrophilic cells were very small in number, and invariably occurred singly among other epithelial cells (Figs. 9 through 11). The cells in the endocervical glands extended frequently their cytoplasmic processes to the surfaces of the glandular lumens. The 19 cervices found to contain the argyrophilic cells were further studied by the Fontana-Masson argentaffin method, but no argentaffin cells were present in the 19 cervices.

Electron Microscopic Findings. Qualitatively, the 3 tumors showed similar ultrastructural characteristics, although there were some quantitative differences.

The most striking feature of the cytoplasm of the 3 tumors was the presence of neurosecretory-type granules. The granules were round with an electron-dense core, enclosed by a limiting membrane and separated from the latter by a narrow, electron-lucent halo. The diameter of the cores varies from 60 mμ to 350 mμ, with a mean of about 180 mμ in Case 2, and about 140 mμ in Cases 1 and 3 (Figs. 12 through 18). The number of the granules varied widely in different tumors, and even in cells within the same tumors. Every tumor cells of Cases

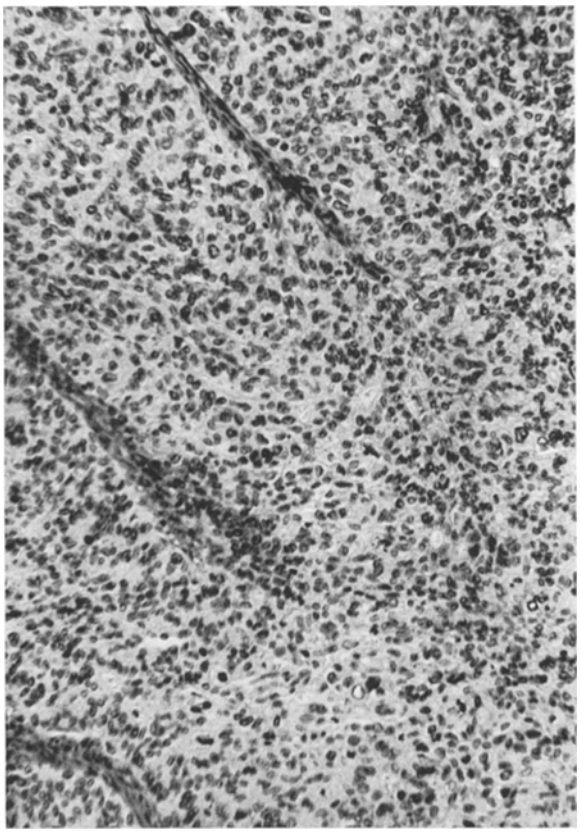


Fig. 3. Case 5. Diffuse cell nests composed of polyhedral cells. A large number of intercellular spaces are present (H and E, ×350)

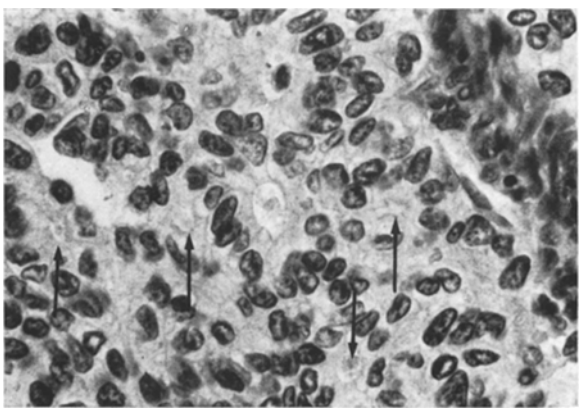


Fig. 4. Case 5. Higher magnification of Fig. 4. Ill-defined and well-defined intercellular spaces (arrows) are noted (H and E, ×1100)

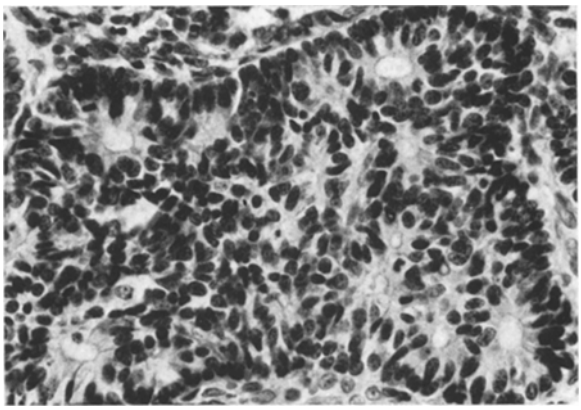


Fig. 5. Case 2. Tumor cell nest shows rosettes and gland-like lumens (H and E, ×1200)

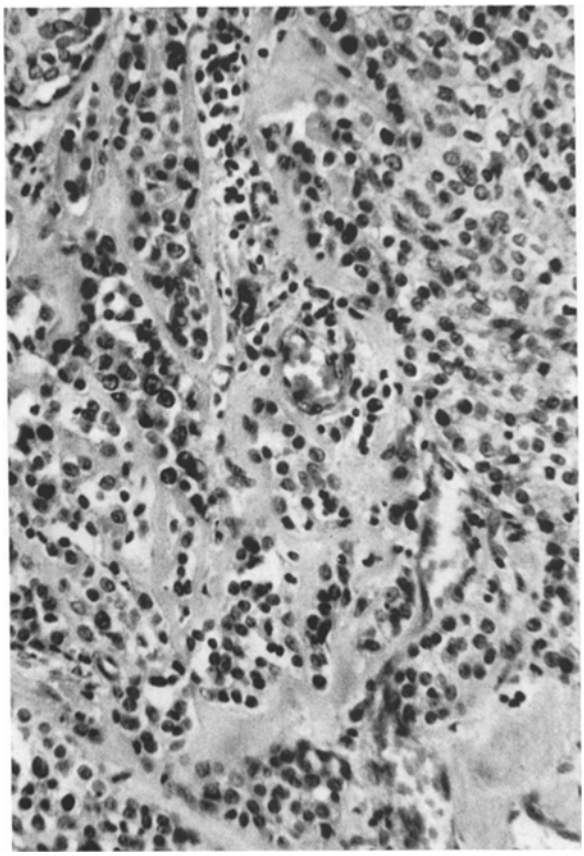


Fig. 6. Case 5. Tumor cell nests with broad, hyalinized stroma negative for Congo red reaction (H and E, ×740)

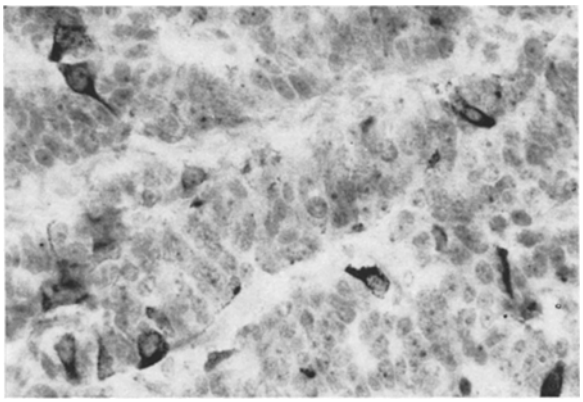


Fig. 7. Case 2. Several tumor cells filled with argyrophil granules are present. Some of them show dendrite-like cytoplasmic processes (Grimelius stain, ×1350)

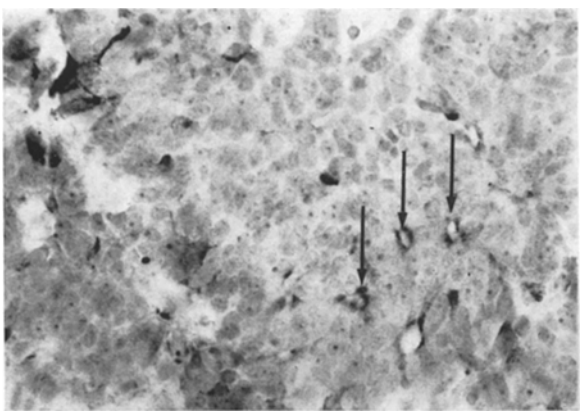


Fig. 8. Case 2. Argyrophil granules are accumulated in the apical cytoplasm of the tumor cells forming the rosettes (arrows). An argyrophil tumor cell with dendrite-like processes is noted (Grimelius stain, ×1350)

1 and 2 contained varying numbers of the granules, while about half of the tumor cells in Case 3 contained them in lesser numbers. The distribution of the granules, as a rule, was random and uniform throughout the cytoplasm. The alignment of the granules along the cell membranes was occasionally observed.

Another striking feature, most notable in Case 2, was the presence of intracytoplasmic microfilaments. Many of the tumor cells in each tumor showed an abundance of intracytoplasmic microfilaments (Figs. 13, 14 and 16). Although in many instances the microfilaments were finely scattered throughout the cytoplasm, they were occasionally arranged in parallel bundels, often located in a perinuclear area (Fig. 16). The microfilaments were never demonstrated to condense, nor were they seen to terminate in attachment devics.

Nuclei were generally elongated with a markedly irregular margin, and showed numerous areas of chromatin clumping scattered throughout the nucleoplasm

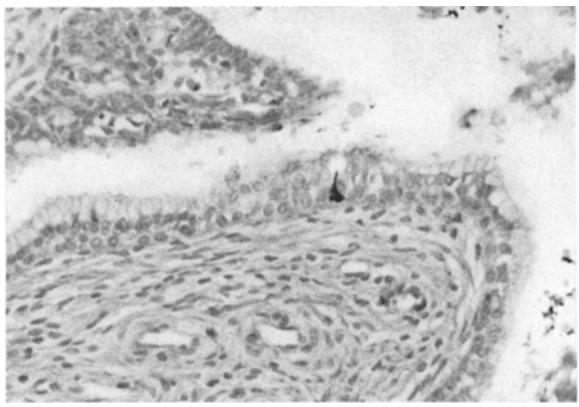


Fig. 9. An argyrophil cell among the columnar cells of the gland (Grimelius stain, ×500)

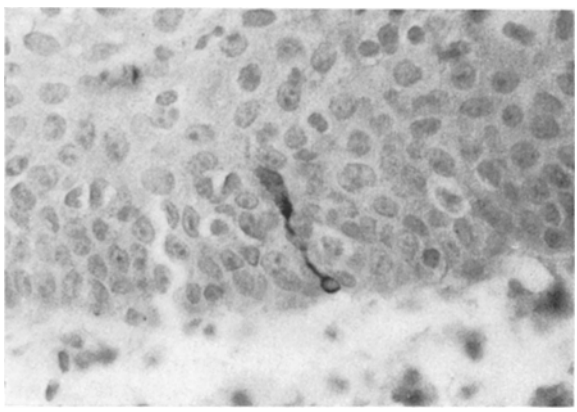


Fig. 10

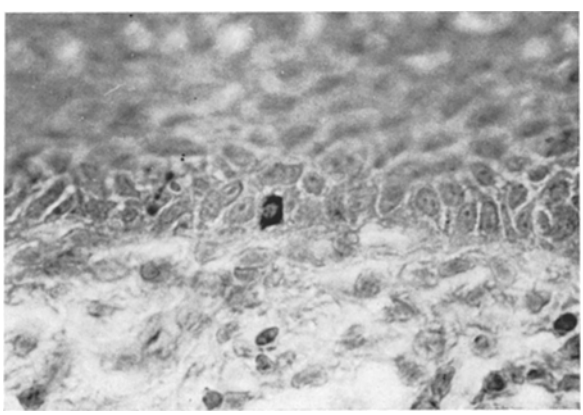


Fig. 11

Figs. 10 and 11. Argyrophil cells are located among the basal cells of the squamous epithelium of the cervix (Grimelius stain, ×1600 each)

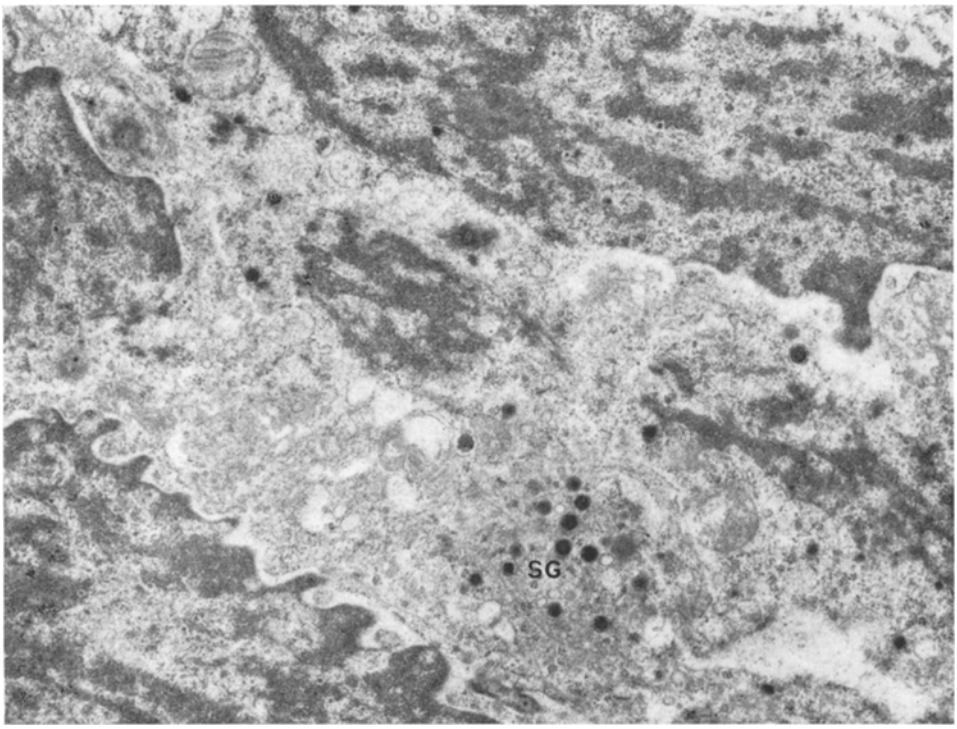


Fig. 12. Case 1. Electron micrograph showing a cluster of neurosecretory-type granules (*SG*) within cytoplasm of a tumor cell. Irregularly shaped nuclei exhibit numerous areas of chromatin clumping and wavy outlines (×12500)

(Fig. 12). A few cells showed ovoid nuclei with a homogenous chromatin distribution (Fig. 17). Free ribosomes were distributed throughout the cytoplasm. Rough and smooth surface endoplasmic reticulum profiles were sparse. Mitochondria were abundant, mostly spherical, with a pale matrix and few cristae. Golgi complexes were not prominent. Microtubules were frequently observed in the 3 tumors.

Intercellular connections showed occasional invaginations of the plasma membranes but otherwise uncomplicated. Desmosomal attachments were rarely seen. Arrangement of tumor cells in rosettes was encountered in Case 2. The tumor cells forming the rosettes were adherent at their apical regions by the junctional complexes (Fig. 18). The apical borders of the cells had varying numbers of microvilli or microvilli-like cytoplasmic processes projected into the lumens that contained fine granular material of low electron density.

Six examples of squamous carcinoma were also examined and no neurosecretory-type granules were detected.

Discussions

Although carcinomas of the cervix have generally been classified into squamous and adenocarcinomas, the 5 tumors presented in this report differ from either type in the microscopic, electron microscopic, and cytochemical features.

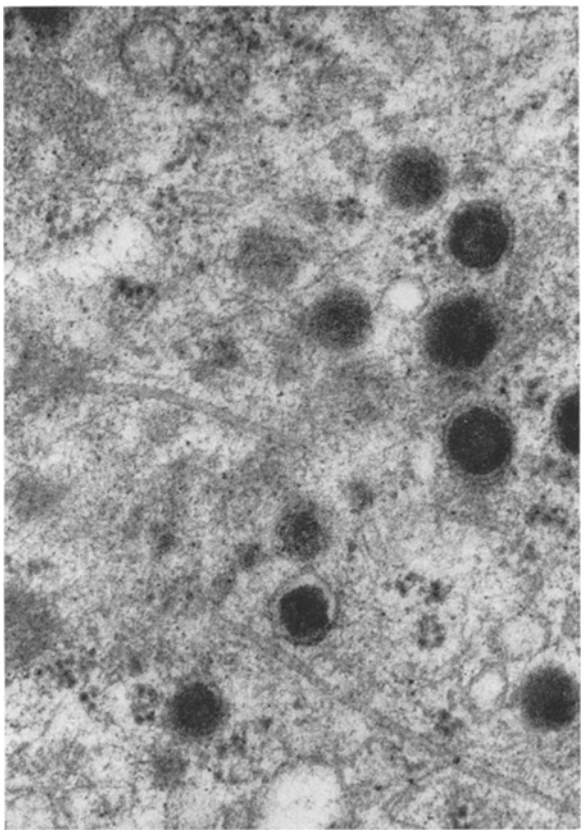


Fig. 13. Case 1. Higher magnification of Fig. 12 showing dense core granules with unit membranes. Microtubules and finely distributed microfilaments are present (×67500)

Microscopically, these 5 tumors are characterized by the formation of solid-sheets, ribbons, streams and rosettes. These microscopic characteristics are well consistent with those already given by other authors for a variety of endocrine polypeptide tumors (apudomas) that arise from the cells of the APUD series (Hazard *et al.*, 1959; Freeman *et al.*, 1965; Williams *et al.*, 1966; Soga *et al.*, 1971; Tateishi *et al.*, 1972; Greider *et al.*, 1974), and for oat cell carcinomas of the lung (Azzopardi, 1959; Kozlowski *et al.*, 1970).

The similarity between the presented tumors and apudomas is further emphasized by the ultrastructural observations reported here and the prior electron microscopic studies made on apudomas in different organs. By electron microscopy, the 5 tumors are characterized by the presence of neurosecretory-type granules, the abundance of intracytoplasmic microfilaments, the absence of tonofilaments, and the paucity of desmosomal attachments. The presence of neurosecretory-type granules is the constant and principal feature of the tumor cells of apudomas as well as the cells of the APUD series.

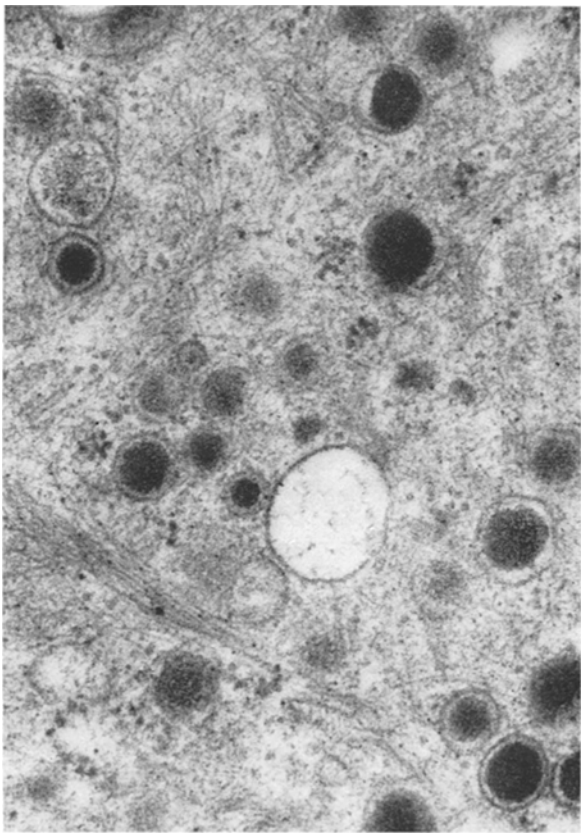


Fig. 14. Case 1. Cytoplasm of another tumor cell containing a cluster of neurosecretory-type granules. Microfilaments are finely scattered throughout the cytoplasm (×60000)

The abundance of intracytoplasmic microfilaments can be interpreted as an evidence of a relationship between the presented tumors and apudomas. The presence of abundant microfilaments in the cytoplasm of the tumor cells has been observed in thyroid medullary carcinoma (Horvath *et al.*, 1972), carcinoids (Luse and Lacy, 1960; Johnston and Waisman, 1971), and pancreatic islet-cell tumor (Greider and Elliott, 1964). Studies by Pearse (1969) have suggested that the formation of fine, intracytoplasmic microfilaments and of microtubules are of the distinctive characteristics of polypeptide-hormone secreting cells of the APUD series.

The present work shows that argyrophil cells are normal, but scanty inhabitants of the cervical mucosa, and shows also the occurrence of argyrophil cells within the tumors. From the morphologic, and cytochemical observations of the 5 tumors presented here, together with the identification of the argyrophil cells in the cervical mucosa, it seems likely that the 5 tumors may well be a specific type of tumors that arise from the argyrophil cells in the cervix. They should be regarded

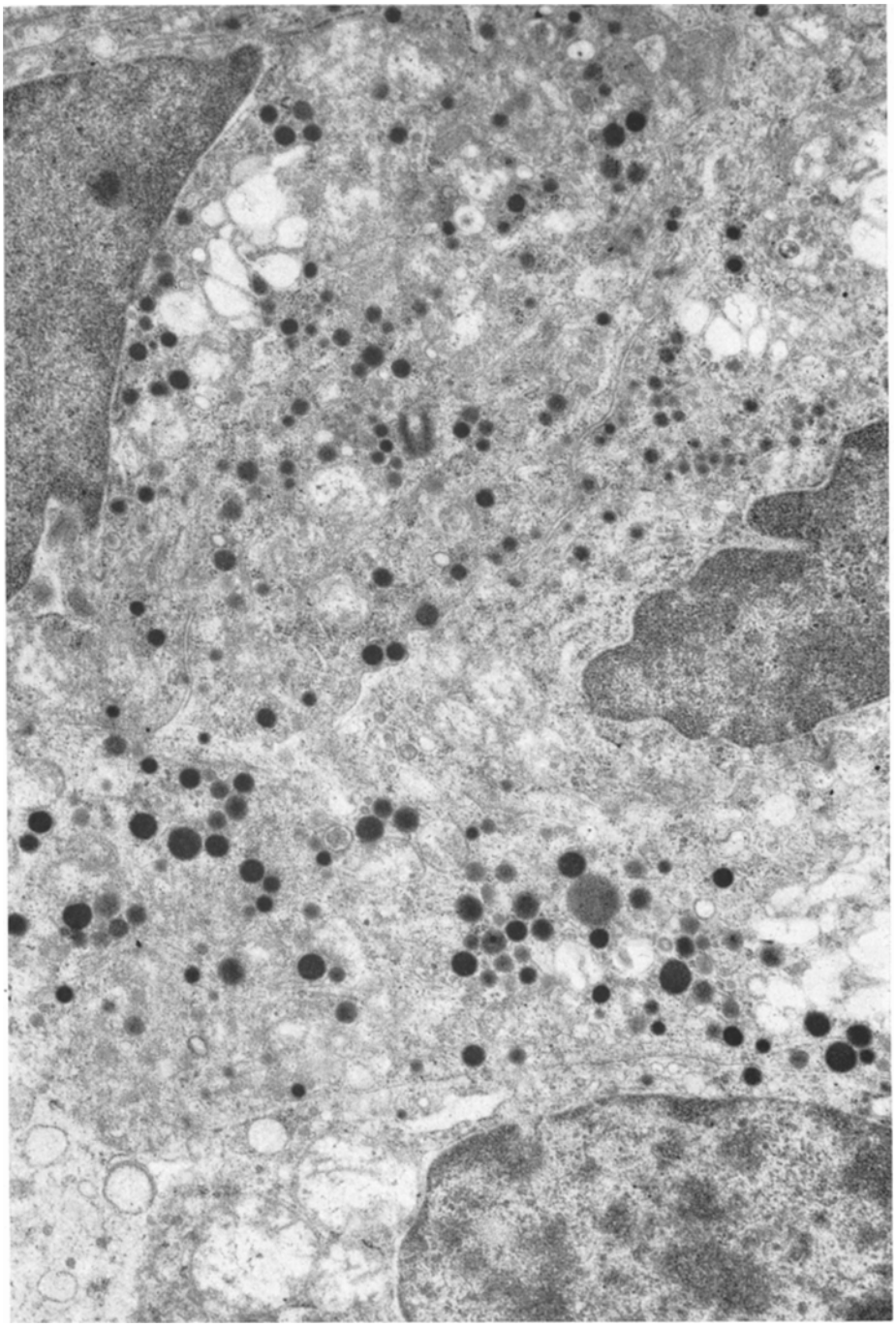


Fig. 15. Case 2. Electron micrograph shows tumor cells containing a large number of neurosecretory-type granules. The granules vary in size and in electron density. Some of them lie along the plasma membranes (×15000)

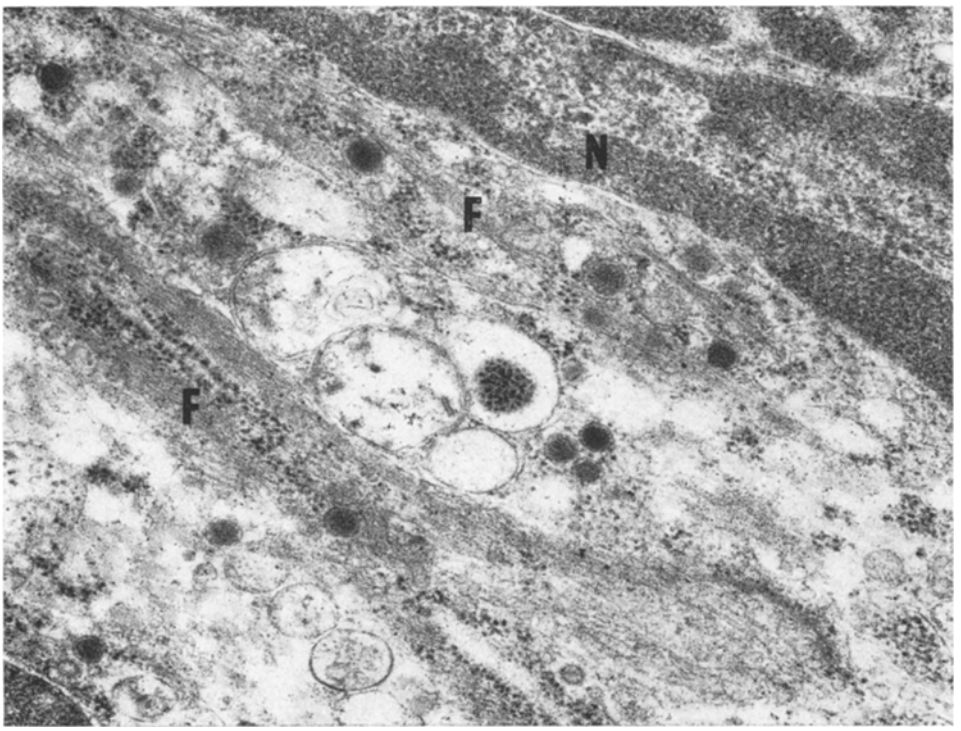


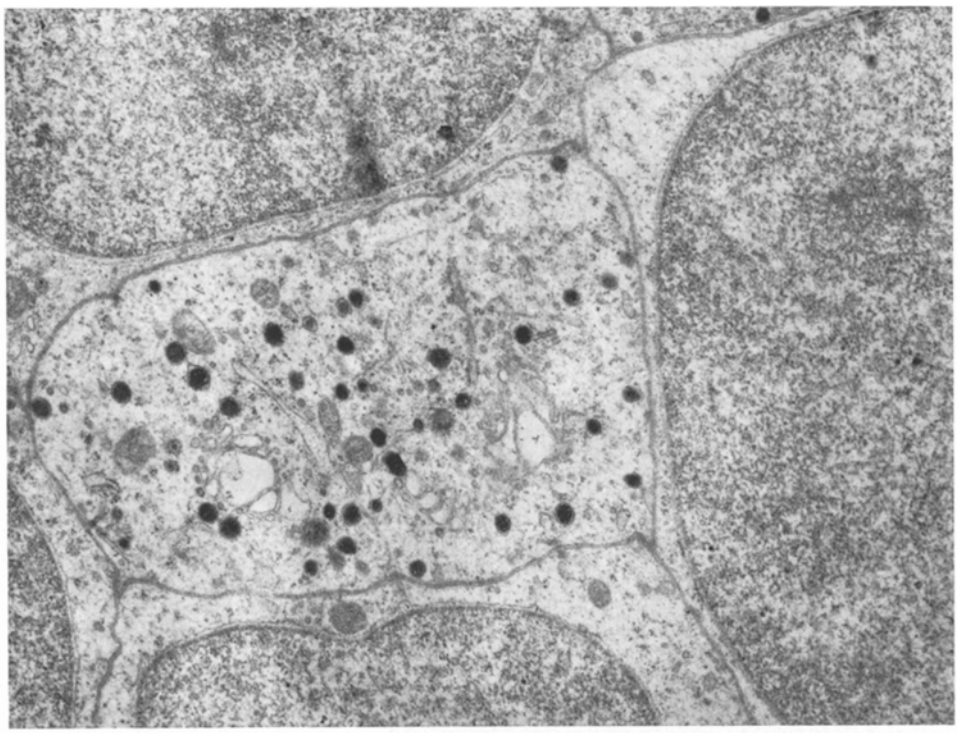
Fig. 16. Case 2. A tumor cell containing bundles of intracytoplasmic microfilaments (*F*) and neurosecretory-type granules (*N*: Nucleus, ×40000)

as a member of apudomas, and could have a biological activity as a functioning tumor, though no suitable hormone has yet been identified for their parent cells.

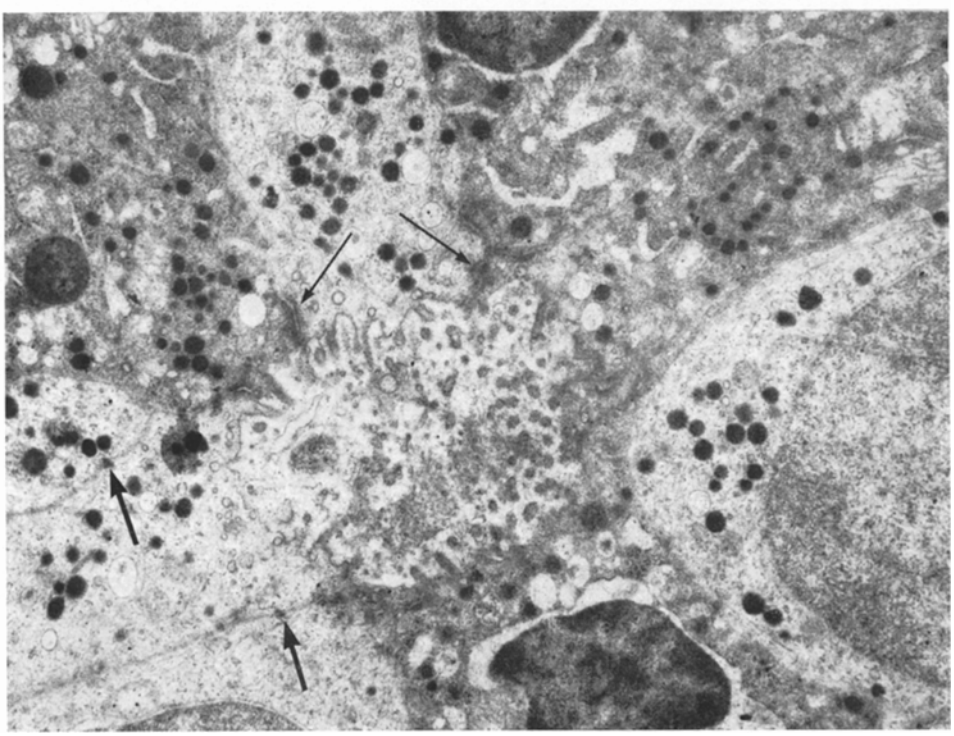
Although small cell carcinomas of the cervix are generally accepted as an anaplastic variant of other types of cervical carcinoma, the present work suggests that some of them are of endocrine origin just as are oat cell carcinomas of the lung. During the past few years, evidences have accumulated to show that oat cell carcinomas of the lung are derived from the argyrophil cells in the bronchial trees, and that they are not an anaplastic variant of squamous or adenocarcinomas of the lung, but a more malignant counterpart of bronchial carcinoids (Bensch *et al.*, 1968; Hattori *et al.*, 1968, 1972; Tateishi, 1973). When the tumors presented

Fig. 17. Case 2. Oval nuclei show a homogenous chromatin distribution. Neurosecretory-type granules are accumulating within cytoplasmic process of a tumor cell. No desmosomes are present (×20000)

Fig. 18. Case 2. A rosette with microvilli projecting into the lumen. Junctional complexes (thin arrows) are present in the juxtaluminal region. Desmosomal attachments (broad arrows) are observed. A large number of neurosecretory-type granules are concentrated in the apical cytoplasm of the cells forming the lumen



17



18

in this paper were composed predominantly of small cells as in Cases 1 and 2, the microscopic similarity to oat cell carcinoma of the lung is striking. Small cell carcinomas identical in structure to oat cell carcinomas of the lung may occur wherever argyrophil cells are present. Extrapulmonary sites are the esophagus (McKeown, 1952; Taniguchi *et al.*, 1973; Watanabe *et al.*, 1974), thymus (Cohen *et al.*, 1960), and pancreas (Corrin *et al.*, 1973), where argyrophil cells have been shown to be normal, but scanty inhabitants in these sites (Rosai and Higa, 1972; Tateishi *et al.*, 1974). Small cell carcinomas reported in these sites occasionally elaborated ACTH as just often did oat cell carcinomas of the lung. These small cell carcinomas may be accepted as an example of the specific type tumor derived from the argyrophil cells in these sites.

The normal function of the argyrophil cells in the cervix is quite unknown, although they seem to be a member of the APUD series. It has been suggested that a sole common function of the cells of this series is the production of a low molecular weight polypeptide hormone (Pearse, 1969, 1972b). Therefore, the possible function of the argyrophil cells in the cervix is the production of a polypeptide hormone, yet unknown at the present time. In the regard, biochemical studies on a fresh tumor tissue may throw light on the normal function of the argyrophil cells.

Carcinomas of the cervix with the production of a polypeptide hormone are quite rare. So far as we are aware, there is only one previously reported case of such tumors. Kiang and co-workers (1973) reported a 25-year-old woman who had a carcinoma of the cervix associated with the elevation of immunoassayable insulin in both the serum and tumor extract. While the microscopic diagnosis of their case was a squamous carcinoma, we feel it more likely that the case might be an example identical to our cases. Shames and co-workers (1968) reported a 23-year-old woman who developed a bronchial carcinoid with the production of insulin. As stated by Kiang (1973), it is of interest that the initial clinical diagnosis of the case was a carcinoma of the cervix with a microscopic diagnosis of Grade III squamous carcinoma. From the clinical records of the case, it is impossible to avoid the impression that the case was an endocrine tumor originating in the cervix.

The morphological and cytochemical features of the 5 tumors presented in this paper are sufficiently distinctive to permit recognition of an additional type for the classification of carcinoma of the cervix. Among the possible designations of this specific type of tumors, which include medullary carcinoma, oat cell carcinoma, small cell carcinoma, carcinoid, and argyrophil cell carcinoma, we prefer the term "argyrophil cell carcinoma" that seems to represent suitably the specific features of these tumors; the varied microscopic features, the histogenesis, and the possible endocrine function.

This study is supported by a Grant-in-Aid for cancer research from the Ministry of Education, Japan and The Osaka Association for Prevention of Adult Diseases.

The authors are grateful to Mrs. M. Okada for her electron microscopic technical assistance.

References

Albores-Saavedra, J., Poucell, S., Rodriguez-Martinez, H. A.: Primary carcinoid of the uterine cervix. Sobreitiro de Pathologia **10**, 185–193 (1972)

Azzopardi, J. G.: Oat cell carcinoma of the bronchus.: J. Path. Bact. **78**, 513–519 (1959)

Bensch, K. G., Corrin, B., Pariente, R., Spencer, H.: Oat-cell carcinoms of the lung. Its origin and relationship to bronchial carcinoid. Cancer (Philad.) **22**, 1163–1172 (1968)

Cohen, R. B., Toll, G. D., Castleman, B.: Bronchial adenoma and Cushing's syndrome. Their relation to thymomas and oat cell carcinomas associated with hyperadrenocorticism. Cancer (Philad.) **13**, 812–817 (1960)

Corrin, B., Gilby, E. D., Jones, N. F., Patrick, J.: Oat cell carcinoma of the pancreas with ectopic ACTH secretion. Cancer (Philad.) **31**, 1523–1527 (1973)

Feyrter, F.: Zur Pathologie des Urogenital Helle-Zellen-Systems. Virchows Arch. path. Anat. **320**, 564–576 (1951)

Fox, H., Kazzaz, B., Langley, F. A.: Argyrophil and argentaffin cells in the female genital tract and in ovarian mucinous cysts. J. Path. Bact. **88**, 479–488 (1964)

Freeman, D., Lindsay, S.: Medullary carcinoma of the thyroid gland. A clinicopathological study of 33 patients. Arch. Path. **80**, 575–582 (1965)

Greider, M. H., Elliott, D. W.: Electron microscopy of human pancreatic tumors of islet cell origin. Amer. J. Path. **44**, 663–678 (1964)

Greider, M. H., Rosai, J., McGuigan, J. E.: The human pancreatic islet cells and their tumors. II. Ulcerogenic and diarrheogenic tumors. Cancer (Philad.) **33**, 1423–1443 (1974)

Grimelius, L.: Silver nitrate stain for α 2 cells in human pancreatic islets. Acta Soc. Med. upsalien. **73**, 243–270 (1968)

Hattori, S., Matsuda, M., Tateishi, R., Nishihara, H., Horai, T.: Oat-cell carcinoma of the lung. Clinical and morphological studies in relation to its histogenesis. Cancer (Philad.) **30**, 1014–1024 (1972)

Hattori, S., Matsuda, M., Tateishi, R., Tatsumi, N., Terazawa, T.: Oat-cell carcinoma of the lung containing serotonin granules. Gann **59**, 123–129 (1968)

Hazard, J. B., Hawk, W. A., Crile, G., Jr.: Medullary (solid) carcinoma of the thyroid. A clinicopathologic entity. J. clin. Endocr. **37**, 205–209 (1959)

Horvath, E., Kovacs, K., Ross, R. C.: Medullary cancer of the thyroid gland and its possible relations to carcinoid. Virchows Arch. Abt. A **356**, 281–292 (1972)

Johnston, W. H., Waisman, J.: Carcinoid tumor of the vermiform appendix with Cushing's syndrome. Ultrastructural study of a case. Cancer (Philad.) **27**, 681–686 (1971)

Kiang, D. T., Bauer, G. E., Kennedy, B. T.: Immunoassayable insulin in carcinoma of the cervix associated with hypoglycemia. Cancer (Philad.) **31**, 801–805 (1973)

Kozlowski, H., Hrabowska, M., Polonski, R.: Amyloid-ähnliche Ablagerungen in Lungenkarzinom- und Bronchialadenomfällen. Arch. Geschwulstforsch. **36**, 370–384 (1970)

Luse, S. A., Lacy, D. E.: Electron microscopy of a malignant argentaffin tumor. Cancer (Philad.) **13**, 334–346 (1960)

McKeown, F.: Oat-cell carcinoma of the esophagus. J. Path. Bact. **64**, 889–891 (1952)

Pearse, A. G. E.: 5-hydroxytryptophan uptake by dog thyroid C cells and its possible significance in polypeptide hormone production. Nature (Lond.) **211**, 598–600 (1966)

Pearse, A. G. E.: Common cytochemical and ultrastructural characteristics of cells producing polypeptide hormones (The APUD series) and their relevance to thyroid and ultimobronchial C cells. Proc. roy. Soc. B **170**, 71–80 (1968)

Pearse, A. G. E.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. J. Histchem. Cytochem. **17**, 303–313 (1969)

Pearse, A. G. E.: Histochemistry, theoretical and applied, 3rd ed., vol. 2. London: Churchill-Livingstone 1972

Pearse, A. G. E., Ewen, S. W. B., Polak, J. M.: The genesis of apudamyloid in endocrine polypeptide tumors. Histochemical distinction from immunamyloid. Virchows Arch. Abt. B **10**, 93–107 (1972)

Puchtler, H., Sweat, F., Levine, M.: On the binding of Congo red by amyloid. J. Histochem. Cytochem. **10**, 355–364 (1962)

Rosai, J., Higa, E.: Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. Cancer (Philad.) **29**, 1061–1074 (1972)
Shames, J. M., Dhurandhar, N. R., Blackard, W. G.: Insulin-secreting bronchial carcinoid tumor with widespread metastases. Amer. J. Med. **44**, 632–637 (1968)
Soga, J., Tazawa, K.: Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases. Cancer (Philad.) **28**, 990–998 (1971)
Sziji, I., Csapó, Z., László, F. A., Kovács, K.: Medullary cancer of the thyroid gland associated with hypercorticism. Cancer (Philad.) **24**, 167–173 (1969)
Taniguchi, K., Iwanaga, T., Kosaki, G., Horai, T., Sano, M., Tateishi, R., Taniguchi, H.: Oat-cell carcinoma of the esophagus producing ACTH. Report of 2 cases (in Japanese). Saishin-Igaku **28**, 1834–1837 (1973)
Tateishi, R.: Distribution of argyrophil cells in adult human lungs. Arch. Path. **96**, 198–202 (1973)
Tateishi, R., Takahashi, Y., Noguchi, A.: Histologic and ultracytochemical studies on thyroid medullary carcinoma. Diagnostic significance of argyrophil secretory granules. Cancer (Philad.) **30**, 755–763 (1972)
Tateishi, R., Taniguchi, H., Wada, A., Horai, T., Taniguchi, K.: Argyrophil cells and melanocytes in esophageal mucosa. Arch. Path. **98**, 87–89 (1974)
Watanabe, H., Karasawa, K., Okada, Y., Akamine, Y., Kobayashi, S., Ariyoshi, H., Sato, T., Suchi, T., Hosoda, S., Susuki, H., Kito, H.: Carcinoid and oat-cell carcinoma of esophagus. With emphasis on close relationship between both tumors. [In Japanese.] Jap. J. Cancer Clin. **20**, 181–190 (1974)
Williams, E. D., Brown, C. L., Doniach, I.: Pathological and clinical findings in a series of 67 cases of medullary carcinoma of the thyroid. J. clin. Path. **19**, 103–113 (1966)

Ryuhei Tateishi, MD
Department of Pathology
The Center for Adult Diseases, Osaka
Nakamichi 1-3-3, Higashinari,
Osaka, Japan