

The Dynamic Histopathologic Spectrum of Lung Cancer

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The APUD concept has postulated that pulmonary carcinoids and small cell carcinomas arise from the neural crest. Its development from hypothesis to tautology is traced, and evidence is presented that all pulmonary epithelial tumors arise from the primitive endoderm. Morphologic studies show that a dynamic spectrum exists. Not only do various cell types appear within a single section, but cell types may change from biopsy to autopsy with or without chemotherapy. The spectrum is sustained at the ultramicroscopic level in regard to organelles such as desmosomes, tonofibrils, and dense core granules. Secretory products such as ACTH and L-dopa decarboxylase also show that all lung cancers are related. Epidemiologic evidence indicates that small cell carcinomas in uranium miners occur after prolonged squamous cell dysplasia, and that carcinoids occur independently of external carcinogens, but show transitions to other tumors. Finally, experimental evidence indicates that the K cells, to which carcinoids are most closely related, are of local origin.

The airways of the lung are formed from an endodermal bud, which grows into a tube lined by a single layer of endodermal cells. These cells give rise to all of the lining cells of the respiratory tract (ciliated cells and Type I pneumonocytes) and all of the secretory cells (goblet cells, Clara cells, and Type II pneumonocytes) [1,2]. Bensch et al. [3] in 1965 described the presence of other cells in small numbers in the bronchial tree. They are found adjacent to the basement membrane, are attached to adjacent epithelial cells by scanty but well-developed desmosomes, and have long cytoplasmic processes interposed between adjacent epithelial cells and also reaching the surface. They are well illustrated by Tateishi [4]. Their most striking characteristics are the presence of membrane bound electron-dense granules, generally less than 120 nm in diameter, and with a narrow space between granule and membrane; and argyrophil properties like the Kultschitzky cells (K cells) of the bowel and the beta cells of the pancreatic islets. An Alcian-blue PAS stain of bronchial mucosa shows the goblet cells, ciliated cells, intermediate cells, and basilar cells, but not the K cells, which require silver staining. It has been postulated that they have a sensory function, responding to oxygen levels by regulating airflow. It has also been postulated that these cells are of neuroectodermal origin, having migrated from the neural crest in embryonic life. This is an important concept because of the common properties which these cells have with carcinoids and small cell carcinomas of the lung, i.e., the APUD concept.

The APUD concept was introduced by Pearse in 1966 [5], when he suggested that

the corticotrophs and melanotrophs of the pituitary, the β cells of the pancreas, and the C cells of the thyroid were all derived from a common neural cell. In 1968, he added the endocrine cells of the gastrointestinal tract [6], temporarily assigning the parent cell to the endoderm, but then he and Polak concluded in 1971-72 [7,8] that they were all derived from the neural crest, after LeDouarin and LeLievre [9] had demonstrated that the C cells of the thyroid were of neuroectodermal origin. By 1972 then the APUD concept stated that all the endocrine and paraendocrine cells of the body, tied together by the commonality of amine precursor uptake and decarboxylation properties, i.e., polypeptide secreting, and by the ultramicroscopic presence of dense-core granules, commonly called neurosecretory, were derived from neural crest, and were really modified nerve cells. Since all carcinoids and many small cell carcinomas of the lung display these characteristics, they have been considered "apudomas," of neurocristal and K cell origin, and separate from all other lung cancers. Indeed, the oat cell carcinoma is often regarded as the malignant counterpart of the carcinoid. The suggestion that they have a common ancestral home in the neural crest is enhanced by bronchial biopsy appearances, in which they are commonly found beneath the mucosa rather than in it, and by the occurrence of multiple endocrine tumor syndromes. The highly malignant behavior of small cell carcinomas and their greater sensitivity to chemotherapy and irradiation have helped strengthen the idea of "separateness" of these tumors.

Over the past 24 years I have examined about 15,000 lung cancers histopathologically, including special stains, and for the past 12 years have done routine electron microscopy on lung tumors. I have also carried out certain epidemiologic and hormonal investigations. The evidence, which is outlined below, has convinced me that all lung cancers, including carcinoids and small cell carcinomas, are derived from the primitive endoderm and that the attractive neural crest hypothesis is wrong. Skrabanek [10] has pointed out that since the cytochemical criteria are inconsistent and since the origin from the neural crest cannot be proved, the APUD concept is of little value, and is only a tautological description of a hormone-producing cell.

LIGHT MORPHOLOGY

The presence of tubules and squames in small cell carcinomas have been recognized for over 50 years. There may be true combinations of small cell and squamous cell carcinoma [11], small cell and adenocarcinoma [12], and in fact all three tumor expressions may exist in a single lesion [13]. In addition, transitions exist between small cell carcinomas and carcinoids and between carcinoids and adenocarcinomas in the lung as well as in the colon [14]. Not only do such combinations occur in about 2 percent of primary tumors [12], but either individual type or the same combined pattern may be repeated in the metastases [13]. In fact, tumors which present as pure small cell carcinoma on biopsy may show admixtures of small cell carcinoma with other cell types at autopsy [15,16]. Such evidence strongly points to a common cell of origin for all lung tumors. Figure 1 illustrates a combined small cell-squamous cell carcinoma in the adrenal, metastatic from a similar tumor of the lung in a 40-year-old man. The squamous cell component alone extended to the chest wall. The oat cell component alone metastasized to the brain. Figure 2 illustrates a combined small cell-bronchioloalveolar carcinoma of the lung (case contributed by Dr. R. Tateishi, The Center for Adult Diseases, Osaka, Japan).

ULTRAMICROSCOPIC MORPHOLOGY

In 1968, Bensch et al. [17] demonstrated similar dense core granules in both car-

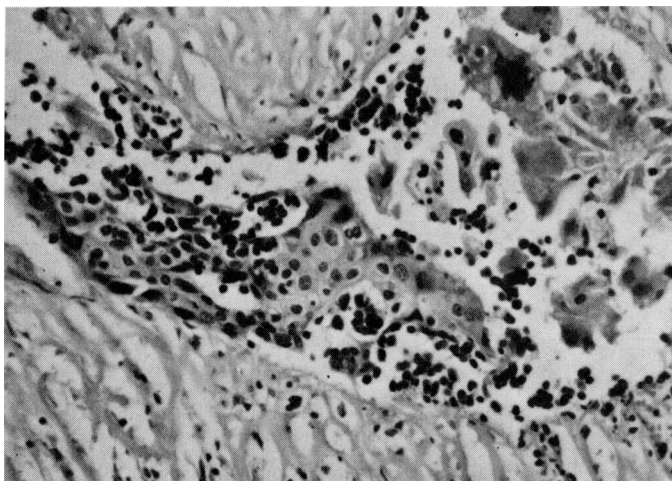


FIG. 1. Combined small cell-squamous cell carcinoma metastatic to the adrenal from a similar tumor in the lung. H&E \times 480.

cinoids and oat cell carcinomas. They noted their development from vesicular Golgi components, found they were more numerous than in K cells, and had a wide range of size from 70 to 500 nm. In oat cell carcinoma, the granules were fewer in number, smaller in size (50 to 240 nm) and present in 1/6 or fewer cells. Since then, the granulation of small cell carcinomas has been studied extensively. In an examination of 47 oat cell carcinomas, Fisher et al. [18] found exceedingly sparse granules measuring 100 to 130 nm, in contrast to the abundant granules in carcinoids. Mackay et al. [19] found only a few small granules, measuring up to 170 nm. Sidhu [20] has studied 43 small cell carcinomas and found scanty granules in about 30 percent of the tumors, with or without a submembranous halo. My experience with 200 small cell carcinomas is similar, and I have also found occasional dense core granules in all types of lung cancer. Geller and Toker [21] and Raikhlin et al. [22] have found dense core granules in association with adenocarcinomas. I have found dense core granules in squamous cells as have Sidhu and Freska [23] and all the ultramicroscopic features of small cell, squamous cell, and adenocarcinoma have been found within individual cells [24,25]. Figure 3 is an electron micrograph of a

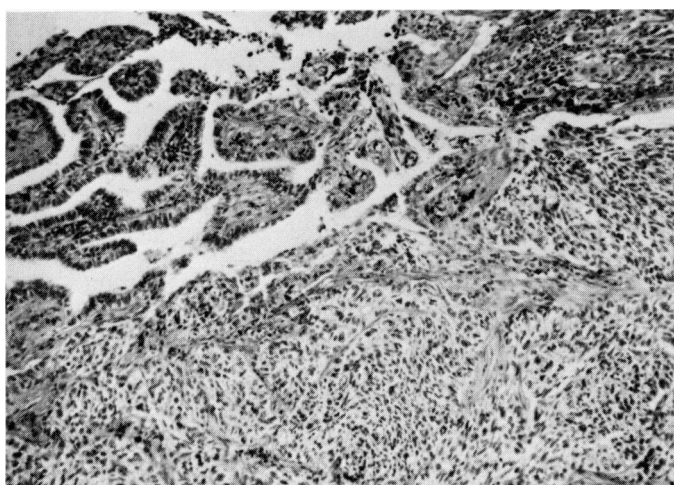


FIG. 2. Combined small cell-bronchioloalveolar carcinoma. H&E \times 100.

nodule in the lung of a 67-year-old man, illustrating membrane-bound dense core granules with submembranous halos. By light microscopy this was a mucin-positive adenocarcinoma. Microvilli projecting into acinar spaces typical of adenocarcinoma were also present in electron micrographs. Figure 4 is an electron micrograph of a cavitated, keratinized, squamous cell carcinoma from the lung of a 54-year-old man. Both well-developed desmosomes with tonofibrils and dense core granules are illustrated. Figure 5 is an electron micrograph of a lung tumor nodule, in which individual cells had moderately abundant cytoplasm, indistinct borders, and prominent nucleoli. The histopathology was interpreted independently by Drs. M. Matthews and R. Yesner as large cell carcinoma. Well-developed desmosomes and dense core granules are illustrated. Dense core granules are largest, most numerous, and most consistent in carcinoids. Figure 6 is an electron micrograph from a peripheral lung tumor in a 51-year-old man. Numerous mitoses were present and liver metastases occurred subsequently. Illustrated are numerous small and large dense core granules measuring up to 500 nm in diameter. This is considered to be a malignant carcinoid. They may appear in combination with mucin granules in carcinoids and in adenocarcinomas, and also in squamous cell carcinomas. Figure 7 is an electron micrograph from a 3 cm nodule in a 60-year-old man, who had a chest film because of hemoptysis. By light microscopy, the tumor was a peripheral carcinoid with a discrete nesting pattern, abundant granular cytoplasm, and prominent nucleoli. Illustrated are abundant dense core granules, well-developed desmosomes with tonofibrils, and numerous multilamellar bodies such as are seen in Type II pneumocytes. Tonofilaments are found in carcinoids [17,19] and tonofibrils in small cell carcinomas [23]. It is clear that dense core granules are not a mark of separateness. It is also of interest that the K cells are attached to the adjacent secretory cells by scanty but well-developed desmosomes, whereas melanocytes, which are known to be derived from neuroectoderm and to migrate to the skin, are not so attached to adjacent cells. No neural connections to K cells have been established. It would appear that the K cell is of local origin.

ARGYROPHILIA

Argyrophilia is related to cells which demonstrate dense core granules. Blondal, Grimelius, et al. [26] found that 46 of 49 tumors diagnosed as carcinoids, were

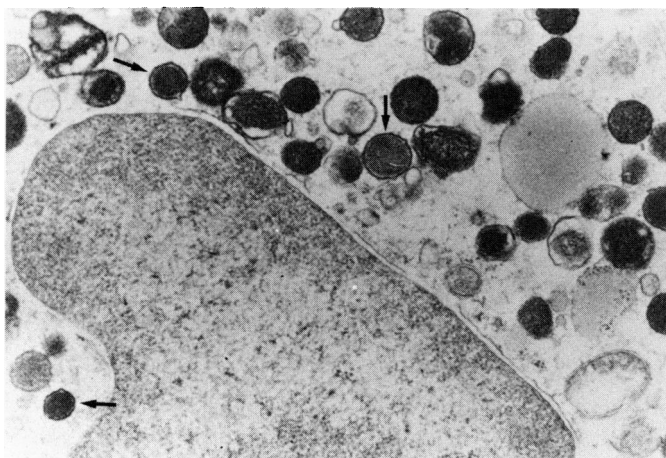


FIG. 3. Mucin positive adenocarcinoma of the lung. Electron micrograph shows numerous dense core granules with submembranous halos (arrows) and other granules which may be lysosomes. $\times 54,000$.

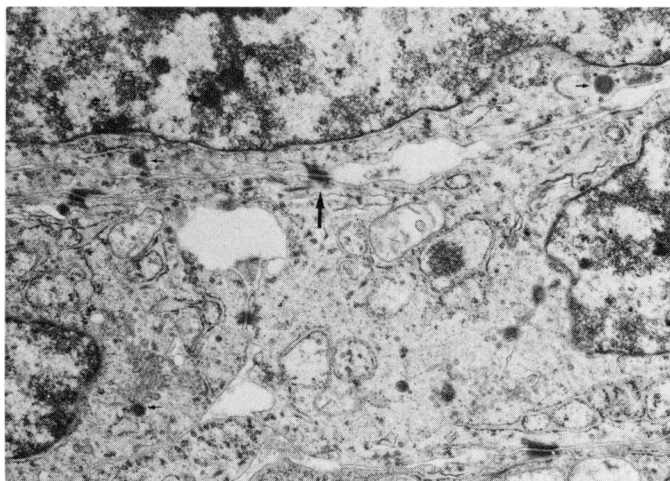


FIG. 4. Keratinized, cavitated, squamous cell carcinoma of the lung. Electron micrograph shows well-developed desmosomes with tonofibrils (*large arrow*) and dense core granules (*small arrows*). $\times 16,000$.

Grimelius (argyrophil) positive. The three non-argyrophil tumors were later reclassified as mucoepidermoid carcinoma, cylindroma, and epidermoid carcinoma. Tateishi [27] found large numbers of argyrophil granules in three carcinoids. I too have found a dozen carcinoids positive, but Fisher [18] found only half of 13 carcinoids positive. On the other hand, there is generally less success with small cell carcinomas. Fisher [18] found a positive argyrophil reaction in 15 percent of his oat cell carcinomas. Tateishi [27] found no argyrophilic granules at all in three of four lymphocyte-like (oat cell) small cell carcinomas, but those of fusiform type had more numerous granules. In our hands, the fusiform pattern of small cell carcinoma frequently occurs as a focal change or in a metastatic site of what is otherwise an oat cell carcinoma, and represents a common pattern with many peripheral carcinoids.

HORMONAL

Gewirtz and Yalow [28] have shown that all lung carcinomas produce big ACTH. I [29] have demonstrated the ACTH content of lung tumor to be highest in oat cell carcinomas (average 27.5 ng/gm), less in intermediate small cell carcinomas (15

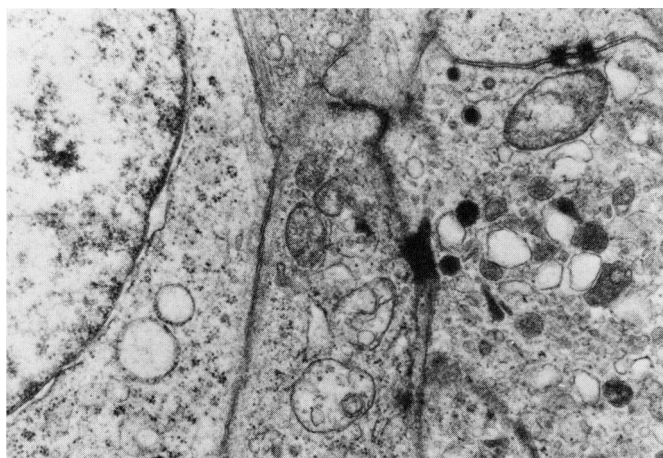


FIG. 5. Large cell carcinoma of the lung. Electron micrograph shows well-developed desmosomes with tonofibrils and typical dense core granules (Contributed by Dr. R.N. Rao, Medical College of Georgia, Augusta). $\times 48,000$.

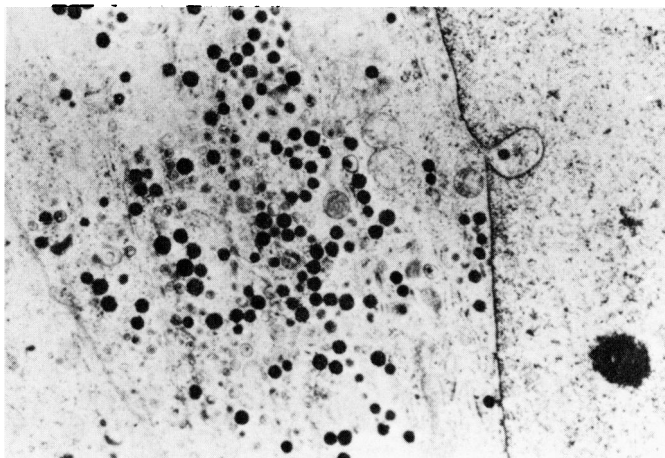


FIG. 6. Malignant peripheral carcinoid of lung, with lymph node and liver metastases. Electron micrograph shows numerous dense core granules (Contributed by Dr. H.E. Graham, V.A.M.C., Dallas, Texas). $\times 16,000$.

ng/gm), still less in large cell carcinomas (6 ng/gm), and least in differentiated squamous cell and adenocarcinomas (2 ng/gm). Tateishi et al. [27] have found no correlation between the number of argyrophil cells and the number of granules or the amount of either ACTH or serotonin in tumor extracts. Calcitonin is also produced by all cell types but most abundantly by small cell carcinomas [30]. Inappropriate antidiuretic hormone also occurs most frequently with small cell carcinoma but also occurs with other cell types [31]. Baylin et al. [32] have found that L-dopa decarboxylase, an enzyme essential in the APUD concept, is not restricted to small cell carcinoma. Again, the hormonal evidence is strong that all lung carcinomas are related.

EPIDEMIOLOGY

It has been known for half a century that there is an exceptionally high rate of small cell carcinomas among miners exposed to radioactivity [33,34]. I have reviewed slides provided by Saccomanno from the Colorado miners and confirmed

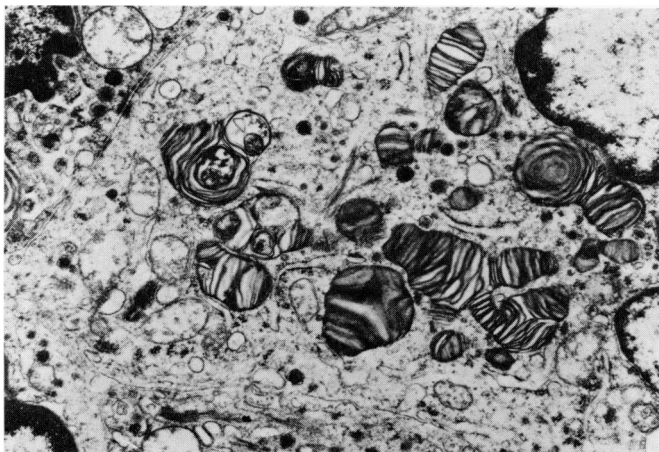


FIG. 7. Peripheral carcinoid of the lung. Electron micrograph shows abundant typical dense core granules, well-developed desmosomes, and numerous multilamellar bodies (Contributed by Dr. K. Yoneda, V.A.M.C., Lexington, Kentucky). $\times 36,000$.

that 66 percent of them were small cell carcinomas. Yet Saccomanno [35] has demonstrated, by serial pulmonary cytology studies, that the miners had gone through stages of squamous dysplasia and carcinoma-in-situ previously. This is striking evidence of the relationship of small cell carcinomas to the bronchial epithelium. It is inconceivable to me that so many small cell carcinomas could have arisen from the few K cells scattered through the adult human bronchus. It is also of great interest that the percentage of small cell carcinomas has fallen to the average (approximately 20 percent) encountered among non-uranium miners since good prophylactic procedures have been installed [36]. Although not as potent as uranium daughters, amount of cigarette smoking alone may increase the percentage of small cell carcinoma. Yesner et al. [37] and Auerbach et al. [38] have found that heavy smokers have more small cell carcinomas than light smokers. Huhti et al. [39] have found that age of onset is important, i.e., that more small cell carcinomas occur among those who start smoking at a younger age. Weiss [40] has not found any relationship between cell type and amount smoked. No carcinoma-in-situ stage of small cell carcinoma is known to exist. Saccomanno's careful work seems to indicate that the small cell carcinomas which have been so prevalent in uranium miners are preceded by dysplasia and carcinoma-in-situ indistinguishable from that which occurs in squamous cell carcinoma. Furthermore, this seems more likely to occur with the greater degree of carcinogenicity in exposure to uranium daughters and heavy smoking. The epidemiologic relationship of carcinoids to small cell carcinomas is quite different. Carcinoids are less than half as numerous as small cell carcinomas, occur in a younger population, and have no known relationship to cigarette smoking, uranium mining, asbestos, or other industrial agent. In the past, the female/male ratio has been higher than in other lung tumors, and they are peripheral as often as central. Their capacity for metastasis is low. Blondal et al. [26] reported 4 percent dying of metastases, but none after lobectomy, and an overall ten-year survival rate of over 90 percent. This is in sharp contrast to the over 90 percent metastatic rate of small cell carcinomas with a negligible ten-year survival rate. The carcinoid appears to be essentially an adenoma of K cells in its biologic behavior. A small number show transitions to small cells by light microscopy and ability to metastasize. These have been referred to as malignant carcinoids.

EXPERIMENTAL

The origin of K cells in bronchi from neuroectoderm is totally unproven. Neural connections to the surface of these cells have not been found [3]. On the other hand, it has been proved by Fontaine and LeDouarin [41] that at an early stage, when it is possible to recognize colonization of the enteric ganglia from the neural crest, no such colonization occurs in the bowel endoderm. They did this by the use of quail-chick chimaeras in which quail and chick cells can be separately recognized. Argentaffin cells are found in polypoid adenomas and adenocarcinomas of the bowel in both humans and experimental animals, and in their transplants [42,43] indicating common precursors with other epithelial cells. This is strengthened by the presence of focal collections of argentaffin cells at the free surface in some adenomas [43]. These cells are found only at the base of the crypt in normal colonic epithelium and their migration has never been demonstrated [44]. The argentaffin cells of the pancreatic islets (β cells) have also been shown to arise from the local ductular cells by Pour [45] who treated Syrian hamsters with the carcinogen N-nitrosobis (2 oxopropyl) amine. Bonikos et al. [46] exposed segments of rabbit bronchial mucosa in

organ culture to uranyl acetate. After nine weeks the explants showed a continuous lining of normal-appearing ciliated cells on the mucosal surface and underlying basal cells two or three layers thick. In these proliferating basal cells were found dense core cytoplasmic granules of the "neurosecretory" type. All of these pieces of evidence indicate strongly that cells containing "neurosecretory" granules in the lung and gut are of endodermal and not of neuroectodermal origin.

SUMMARY

The morphologic, ultramorphologic, hormonal, epidemiologic, and experimental evidence indicate that all of the cells normally found in the bronchial tree, including the K cells, are of endodermal origin, i.e., originate from the endodermal stem cells. The evidence also indicates that all of the tumors derived from bronchial epithelium are related, i.e., form a spectrum which is dynamic; that is, may evolve toward or away from the oat cell, the squamous cell, or the adenocarcinoma, dependent on therapy, host response, etc. This constitutes the basis of the Y-construct, in which the oat cell carcinoma is at the base, the large cell carcinoma at the fork, and the squamous cell and adenocarcinomas at either arm [29]. Combined cell types involving small cells are relatively unstable, and overlapping cell types are common. Examination of respiratory epithelium shows that mitoses are equally prevalent in the basal cell and intermediate cell layers, which may contain mucin granules. These cells are the genitors of all lung tumors. Clonal heterogeneity of small cell carcinomas of the lung has been demonstrated by flow-cytometric DNA analysis. In the tumors of 29 evaluable patients, only one cell line could be detected in 23 (79 percent) by Vindelov et al. [47]. Evidence of the presence of two tumor cell clones with different ploidy was obtained in six (21 percent). Actual heterogeneity is probably much higher. Other evidence of clonal heterogeneity has been obtained by Netter-sheim [48] in cultured tumors derived from a single cell. Ten clones were made from each of four adenosquamous carcinomas. After reinjection, six were clearly combined and two were clearly squamous, demonstrating the phenotypical instability of the tumor stem cells. One can therefore expect movement along the spectrum dependent on host, degree of insult, and therapy.

REFERENCES

1. Burri PH, Weibel ER: In *The development of the lung*. Edited by WA Hodson. New York, Dekker, 1976
2. Weibel ER, Gehr P, Haies D, et al: *The cell population of the normal lung*. In *Lung cells in disease*. Edited by A Bouhuys. Amsterdam, North-Holland, 1976
3. Bensch KG, Gordon GB, Millar LR: Studies on the bronchial counterpart of the Kultschitzky (argenta-ffin) cell and innervation of bronchial glands. *J Ultrastruct Res* 12:668-686, 1965
4. Tateishi R: Distribution of argyrophil cells in adult human lungs. *Arch Path* 96:198-202, 1973
5. Pearse AGE: Common cytochemical properties of cells producing polypeptide hormones, with particular reference to calcitonin and the thyroid C cells. *Veterinary Record* 79:587, 1966
6. Pearse AGE: Common cytochemical and ultrastructural characteristics of cells producing polypeptide hormones (the APUD series) and their relevance to thyroid and ultimobranchial C cells and calcitonin. *Proceedings of the Royal Society B170:71*, 1968
7. Pearce AGE, Polak JM: Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract. *Gut* 12:783, 1971
8. Pearse AGE, Polak JM: The neural crest origin of the endocrine polypeptide cells of the APUD series. In *Endocrinology 1971*. Edited by S Taylor. London, Heinemann, 1972, p 145
9. LeDouarin N, Lelièvre C: Démonstration de l'origine neurale des cellules à calcitonin du corps ultimobranchial chez l'embryon de poulet. *Comptes-rendus de l'Académie des Sciences* 270:2857, 1970
10. Skrabanek P: APUD Concept: Hypothesis or tautology? *Medical Hypotheses* 6:437-440, 1980

11. Histological typing of lung tumours. World Health Organization, Geneva, 1967
12. Yesner R, Gerstl B, Auerbach O: Application of the W.H.O. classification of lung carcinoma to biopsy material. *Ann Thor Surg* 1 (1):33-49, 1965
13. Yesner R, Carter D: Clinics in Chest Medicine. Lung Cancer: Recent Advances. Edited by R Mathay. Pathology of carcinoma of the lung—Changing patterns. Baltimore, Williams & Wilkins, 1982
14. Warkel LL: Adenocarcinoid, a mucin-producing carcinoid tumor of the appendix: A study of 39 cases. *Cancer* 42:2784-2787, 1978
15. Brereton HD, Matthews MM, Costa J, et al: Mixed anaplastic small-cell and squamous-cell carcinoma of the lung. *Ann Int Med* 88 (6):805-806, 1978
16. Yesner R, Auerbach O, Gerstl B: Evolution of small cell carcinoma of the lung. *Chest* 76 (3):370, 1979
17. Bensch KG, Corrin B, Pariente R, et al: Oat cell carcinoma of the lung, its origin and relationship to bronchial carcinoid. *Cancer* 22:1163-1172, 1968
18. Fisher ER, Palekar A, Paulson JD: Comparative histopathologic, histochemical, electron microscopic and tissue culture studies of bronchial carcinoids and oat cell carcinomas of the lung. *Am J Clin Path* 69 (2):165-172, 1978
19. Mackay B, Osborne BM, Wilson RA: Ultrastructure of lung neoplasms. In *Lung Cancer*. Edited by MJ Straus. New York, Grune & Stratton, 1977, pp 71-84
20. Sidhu GS: The ultrastructure of malignant epithelial neoplasms of the lung. *Pathol Ann*, 1981. Edited by Sommers and Rosen. In press
21. Geller SA, Toker C: Pulmonary adenomatosis and peripheral adenocarcinomas of the lung. *Arch Path* 88:148, 1969
22. Raikhlil NT, Warzok R, Smirnowa EA: The histogenesis of small cell bronchial carcinoma. *Zentralbl Allg Pathol* 123 (3):202-209, 1979
23. Sidhu GS, Freska O: Oat cell carcinoma of the lung and colon: Their relationship to the origin of enteric and respiratory APUD cells. *Lab Invest* 38 (3):365, 1978
24. McDowell EM, Trump BF: Pulmonary small cell carcinoma showing tripartite differentiation in individual cells. *Human Pathol* 12 (3):286-294, 1981
25. Horie A, Ohta M: Ultrastructural features of large cell carcinoma of the lung with reference to the prognosis of patients. *Human Pathol* 12 (5):423-432, 1981
26. Blondal T, Grimelius L, Nori E, et al: Argyrophil carcinoid tumors of the lung. *Chest* 78 (6):840-844, 1980
27. Tateishi R, Horai T, Hattori S: Demonstration of argyrophil granules in small cell carcinoma of the lung. *Virchows Arch A Path Anat and Histol* 377:203-210, 1978
28. Gewirtz G, Yalow RS: Ectopic ACTH production on carcinoma of the lung. *J Clin Invest* 53:1022, 1974
29. Yesner R: Spectrum of lung cancer and ectopic hormones. *Pathol Ann*, Pt 1, 13:217-240, 1978. Appleton-Century-Crofts
30. Hillyard CJ, Coombes RC, Greenberg PB, et al: Calcitonin in breast and lung cancer. *Clin Endocrinol* 5 (1):1976
31. Amatruda TT Jr: Nonendocrine secreting tumors. In *Duncan's Diseases of Metabolism*, 7th ed. Edited by PK Bondy, LE Rosenberg. Philadelphia, Saunders, 1974
32. Baylin SB, Abeloff MD, Goodwin G, et al: Activities of L-dopa decarboxylase and diamine oxidase (histaminase) in human lung cancer and decarboxylase as a marker for small (oat) cell cancer in cell culture. *Cancer Res* 40:1990-1994, 1980
33. Pirchan A, Siki H: Cancer of the lung in the miners of Jachysnov (Joachimstal). *Am J Cancer* XVI (4):681-722, 1932
34. Saccomanno G, Archer VE, Auerbach O, et al: Histologic types of lung cancer among uranium miners. *Cancer* 27:515-523, 1971
35. Saccomanno G: Diagnostic pulmonary cytology. Amer Soc Clin Path, Chicago, 1978
36. Saccomanno G: Personal communication
37. Yesner R, Gelfman NA, Feinstein AR: A reappraisal of histopathology in lung cancer and correlation of cell types with antecedent cigarette smoking. *Amer Rev Resp Dis* 107:790-797, 1973
38. Auerbach O, Garfinkel L, Parks VR: Histologic type of lung cancer in relation to smoking habits. Year of diagnosis and sites of metastasis. *Chest* 67 (4):382-387, 1975
39. Huhti E, Sutiven S, Reinilia A, et al: Lung cancer in a defined geographical area: History and histological types. *Thorax* 35 (9):660-667, 1980
40. Weiss W, Boncot KR, Seidman H, et al: Risk of lung cancer according to histologic types and cigarette dosage. *JAMA* 222:799-801, 1972

41. Fontaine J, LeDouarin NM: Analysis of endoderm formation in the avian blastoderm by the use of quail-chick chimaeras. *J Embryol Exp Morph* 4:209-222, 1977
42. McCall DM, Gordon M, Bartoszewicz: Electron microscopic study of adenocarcinoma of the colon transplants in the rat. Unpublished study
43. Kaye GI, Fenoglio CM, Pascal RR, et al: Comparative electron microscopic features of normal, hyperplastic, and adenomatous human colonic epithelium. *Gastroent* 64 (5):926-945, 1973
44. Churg H, Muzel J: The renewal pattern of argentaffin and related cells in the small intestine of the mouse (Abstract). *Anat Rec* 169:293, 1971
45. Pour P: Islet cells as a component of pancreatic ductal neoplasms. I. Experimental study: ductular cells, including islet cell precursors, as primary progenitor cells of tumors. *Am J Path* 90 (2):295-316, 1978
46. Bonikos D, Bensch K, Stettler L, et al: The effect of uranyl acetate on bronchial mucosa in organ culture. *Am J Path* 82 (2), 46a, 1976
47. Vindelov LL, Hansen HH, Christensen IJ, et al: Clonal heterogeneity of small-cell anaplastic carcinoma of the lung demonstrated by flow-cytometric DNA analysis. *Cancer Res* 40:4295-4300, 1980
48. Nettersheim P: Anticarcinogenesis of respiratory cancer in rodent systems. US-Japan Coop Cancer Res Program, 5th Joint Meeting on Lung Cancer, Miami, February 1, 1979