**A Note from History:**
The Saga of Carcinoid and Oat-Cell Carcinoma

Steven I. Hajdu¹ and Ping Tang²
¹Los Angeles, California, ²Pathology Department, University of Rochester, Rochester, New York

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Ever since epithelial tumors were recognized in the early 1800s, the tumors were divided into small-cell and large-cell forms. Pathologists had no difficulty distinguishing the benign and malignant large-cell tumors but they had considerable problems separating benign and malignant small-cell tumors.

In 1907, with the intent to solve the dilemma, Siegfried Oberndorfer (1876–1944) of Germany introduced the term “carcinoid” for small-cell tumors of the intestines [1]. By coining the word “carcinoid,” he implied “carcinoma-like.” A carcinoid tumor resembles carcinomas microscopically but is not a carcinoma. Oberndorfer noted that carcinoids can be single or multiple tumors. They range from a few millimeters to several centimeters in diameter and histologically resemble poorly differentiated (small-cell) adenocarcinoma. He reported that carcinoid tumor cells were polymorphic with granular cytoplasm and prominent nuclei and nucleoli [1].

Oberdorfer pointed out that the mostly round or oval cells were in nests (rosettes), ribbons, tubules, or solid bars embedded in densely fibrous and highly vascular stroma. His initial assertion that carcinoids were benign tumors subsequently proved to be incorrect. This was his own conclusion in 1928 [2]. He admitted that some carcinoids exhibit malignant features and metastasize.

As to cell of origin of carcinoids, there was no precise information available but the general feeling was that cells in the stomach described by Rudolph Heidenhain (1834–1897) of Prussia in 1870 [3] and identified in 1897 in the intestinal mucosa by a Russian, Nikolai Kulchitsky (1856-1925) [4], were the source of carcinoids. Within a few years, the cells were named “enterochromaffin” cells [5] and “argentaffin neuroendocrine” cells [6] due to their endocrine cell appearance with special stains.

In 1926, about the time consensus was reached on the relationship between enterochromaffin or neuroendocrine cells and carcinoids, a hitherto unreported small-cell tumor (“oat-celled sarcoma”) of the mediastinum was reported by W. G. Barnard, a British physician [7]. The term “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure in 1936 [8]. However, the first substantial paper on “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure in 1936 [8]. However, the first substantial paper on “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure in 1936 [8]. However, the first substantial paper on “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure [8]. However, the first substantial paper on “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure [8]. However, the first substantial paper on “oat-cell carcinoma” of the lung appeared the first time in a short article on asbestos exposure [8].
plastic-cell carcinoma," or "spindle-cell carcinoma." In their descriptions of the component cells, McKeown and Liebow commented that the cells in oat-cell carcinoma resemble lymphocytes in size and shape. The cytoplasm is scanty and basophilic. The nuclei are dark, uniform, and generally round, although ovoid or spindle-shaped forms are not uncommon. Palisading of the tumor cells may occur at the margins of the tumor. They mentioned that mitoses are numerous and that microscopic forms transitional to other types of carcinomas can occasionally be seen. Their reports [9,10] warned that primary tumors with similar microscopic features occur at extrapulmonary sites and that pathologists should be alert to recognize that such small-cell tumors may metastasize to the lungs.

In 1959, Azzopardi [11] reported the characteristic overlapping of crushed nuclei and bluish discoloration of the wall of capillary vessels in oat-cell carcinomas. In the 1960s, it became established that the histogenesis of oat-cell carcinoma is distinctly different from that of other pulmonary carcinomas. Bensch et al [12] recognized that oat-cell carcinoma and carcinoid tumors are histogenetically related. The origin of both tumors was traced cytochemically and ultrastructurally to the ubiquitous polypeptide hormone-producing cells of the APUD (amine precursor uptake, decarboxylase) system [13]. These cells are capable of secreting a variety of polypeptide hormones, including catecholamines and 5-hydroxytryptamine.

In 1972, a histologic variant of typical carcinoid tumor—composed of large polymorphic nucleolated cells in gland-like arrangement—was named "atypical carcinoid" by Arrigoni et al [14]. These authors concluded that atypical carcinoids have a worse prognosis than the typical ones. An intermediate polygonal large-cell variant of the typical oat-cell carcinoma was reported in 1977 to show decreased responsiveness to therapy [15]. In our review of 204 carcinoid tumors, we were unable to correlate histopathology with clinical outcome [16]. Others came to a similar conclusion in reference to the intermediate variant of oat-cell carcinoma [17].

The concept emerged that there is a spectrum in cellular composition of carcinoids and oat-cell carcinomas in which the typical (well-differentiated) carcinoid represents one end of the spectrum and the typical small-cell (oat-cell) carcinoma the other end of the spectrum [18,19]. It was proposed that the atypical or intermediate forms are the link between the typical forms. This concept became widely accepted by the 1980s [20-24]. Because of the overlapping microscopic appearance of carcinoids and small-cell (oat-cell) carcinomas, pathologists occasionally over-diagnosed carcinoids as small-cell (oat-cell) carcinoma [16,25].

Half a century after it became known that Kulchitzky cells or enterochromaffin cells are present in every organ and tissue, pathologists and laboratory scientists began to report carcinoids and small-cell (oat-cell) carcinomas—in addition to the lung—at extrapulmonary sites such as the esophagus [9,26-29], salivary glands [30], larynx, pharynx, and nasal cavity [27], breast [27,31], gallbladder [32], pancreas [27,33], colon [34], prostate [35-38], kidney [37], urinary bladder [37,39,40], urethra [41], ovary [42,43], endometrium [44,45], uterine cervix [46-48], and vagina [49,50].

The thymus is a unique extrapulmonary intrathoracic organ composed of epithelial and lymphoid cells. It involutes only partially in about 20% of adults and ectopic remnants behind the sternum and in the lower neck are not uncommon. Therefore, it should be no surprise that the thymus and its remnants are the source of a wide spectrum of tumors, including carcinoids and small-cell (oat-cell) carcinoma [19,51-53]. Since the early 1920s it has been noted that the carcinoid is one of the most common epithelial neoplasms of the thymus [19,52-57]. In a recent study, the thymus was ranked as the third most common site of carcinoids, after the intestines and the lung [58]. It was first observed in 1974 that in certain thymic carcinoids and thymomas, neuroendocrine differentiation is associated with a paraneoplastic syndrome [59], similar to that of pulmonary and extrapulmonary tumors with neuroendocrine differentiation. Recently, antineuronal nuclear antibody and skeletal muscle antibodies were detected in some thymic tumors [60,61]. About 10% of thymic carcinomas in adults are small-cell (oat-cell) carcinomas with neuroendocrine differentiation [62-66] and some of them have dual, carcinoid, or other epithelial components [9,10,63].
The latest immunochemical, biochemical, and serologic studies support the view—held for several decades—that carcinoids and small-cell (oat-cell) carcinomas have a common histogenesis, regardless of their organs of origin. Furthermore, the similar morphologic variations, age distribution, chromogranin, TTF-1, and Ki-67 immunohistochemical reactions, mitotic activity, and association with paraneoplastic syndrome strongly suggest that the link between carcinoids and small-cell (oat-cell) carcinomas is genuine [56,67].

In conclusion, much has been contributed by many pathologists, clinicians, and laboratory scientists to the century-long saga of carcinoid and oat-cell carcinoma. Let us hope that with understanding and proper utilization of the above detailed information, it will not take another century to find the causes and the cure for these crippling and deadly diseases.

References