A Note from History:
The Enigma of Ewing’s Sarcoma

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History teaches that without knowing the cause of a disease, physicians can rarely cure it. This review shows how oncologists, pathologists, and molecular biologists have come near to defying history.

In 1921, James Ewing (1866-1943), Professor and Chairman of Pathology at Cornell University School of Medicine and Consultant Pathologist to The Memorial Hospital for Cancer in New York City, gave a definitive description of a series of bone tumors he called diffuse endothelioma [1]. Ewing had mentioned these tumors in 1919 in the first edition of his seminal text on neoplastic diseases [2]. He acknowledged earlier cases [3-5], but he was undoubtedly the first to focus attention on the characteristic clinical, radiologic, and pathologic features of these rare and deadly bone tumors.

At the time of these publications [1,2], Ewing was a recognized authority on neoplastic diseases. He and two clinicians, Joseph Bloodgood (1867-1935) and Ernest A. Codman (1869-1940), founded the Bone Sarcoma Registry in 1921, and Ewing became a commanding figure in the oncology of bone tumors.

Before Ewing developed an interest in the pathology of neoplasms and became affiliated with The Memorial Hospital for Cancer (where he was chief of pathology and hospital director for three decades, until his retirement in 1939), he was a clinical pathologist at Columbia University. He had written several articles on infectious diseases and he was the author of the first illustrated book on hematology [6].

Fig. 1. James Ewing (1866-1943), circa 1920.

Within a few years after Ewing’s 1921 article on bone sarcomas [1], scores of relevant case reports were published all around the world. In these early reports, the writers agreed on the distinctive clinical, radiologic, and microscopic appearance, as well as the dismal prognosis of these unique bone neoplasms. However, they disagreed as to the cell of origin. In 1928, to limit the proliferation of empirical names, such as endothelioma, perithelioma, endothelial myeloma, reticuloendothelioma, reticular sarcoma, and intramedullary sarcoma, Oberling [7] introduced the term Ewing’s sarcoma, which was a non-committal name in regard to the cell of origin.
By 1949, six years after James Ewing’s death, entire chapters were devoted to Ewing’s sarcoma in two leading textbooks on bone tumors [8,9]. The authors pointed out that Ewing’s sarcoma was a rare malignant bone tumor (one case diagnosed/year/million population in the USA). It generally occurred during the second decade of life (at the time of greatest bone growth), but rare examples could be seen in adults. It struck boys more often than girls and was found almost exclusively in Caucasians. The authors added that >60% of the tumors were located in the pelvis and the tubular bones of the lower extremities, but that all bones of the skeletal system, as well as occasional extraskeletal tissues, could be primary sites. They illustrated the characteristic radiologic appearance of the tumor, with the onion-skin-like periosteal elevation and the cellular composition as seen on histologic sections, needle aspiration smears, and stained tissue culture preparations. The authors did not offer any clue as to the cell of origin but gave a detailed description of the natural history of the tumor from its incipient stage to the metastatic spread to bones and lungs. They commented that Ewing’s sarcomas were fast-growing tumors, but that tumor progression was sometimes interrupted by periods of non-growth and might show a diminution in size. However, such happenings were temporary; ultimately <10% of patients survived for 5 years after surgery and radiation therapy. They added that in about 25% of cases, Ewing’s sarcoma was present in multiple bones, indicating either multicentric intramedullary growth, de novo, or widespread intraskeletal metastases.

By 1956, the occasional presence of rosettes without a central lumen (pseudoneuroblastic or sympatheticic rosettes) was confirmed by Masson [10]. He noted that some of the neoplastic cells assembled in cords with fine cytoplasmic tendrils suggesting neural differentiation, and that intra-cytoplasmic deposit of glycogen was demonstrable by the periodic acid-Schiff reaction. By the 1960s it appeared that practically everything was known about the clinical, radiologic, and microscopic appearance of Ewing’s sarcoma, except its etiology, the cell of origin, and how to achieve better survival [11]. The dismal failure to save lives with surgery and radiation led to introduction, in 1974, of a novel sequential adjuvant therapy with four drugs: adriamycin, cyclophosphamide, dactinomycin, and vincristine [12].

During the past 30 years, other dose-intensive chemotherapeutic regimens have been advocated in combination with radiation and/or surgery. The current experience, at the time of this writing, shows that 60 to 80% of patients with locoregional disease survive for five years and that 10 to 20% of patients with disseminated or multicentric disease in multiple bones, are alive five years after initiation of therapy [13].

While the search for optimal oncologic treatment has continued, pathologists and others clinical scientists using emerging cytogenetic and immunochemical techniques have succeeded in characterizing the neoplastic cells of Ewing’s sarcoma. By these techniques, it became evident that the occasionally observed neural differentiation in Ewing’s sarcoma, occurrence of Ewing’s sarcoma-like neoplasms at extra-skeletal sites, and presence of neuroblastoma-like tumors in soft tissues [14], indicate a common or closely related histogenesis of a number of malignant neoplasms with microscopic features similar to those of Ewing’s sarcoma. Demonstration of reciprocal translocations t(11;22) (q24;q12) EWSR1/FLI1) or t(21;22) (q22;q12) as the result of the exchange of N-terminal portions between the est-family transcription factors FLI1 or ERG and EWSR1 (by cytogenetic techniques and reverse transcriptase PCR reaction or in situ suppression hybridization) left no doubt about the correctness of the above impression [15-18]. The impression is further supported by shared positive immunoreactivity (vimentin, CD99, CD57, synap-tophysin, NSE, neurofilament, neuroectodermal antigen, MIC-2 gene, and integrin link kinase) and similarities in ultrastructure (cytoplasmic glycogen and occasional neurosecretory granules) [19-21].

We conclude that advances in molecular pathology and immunochemistry during the last decade have demonstrated common histogenesis of a group of malignant neoplasms and that Ewing’s sarcoma and primitive neuroectodermal tumor probably represent two end-points of phenotypic differentiation. It is almost embarrassing to admit that after all that has been achieved by so many
clinical scientists, the riddle of Ewing’s sarcoma is not yet completely solved because its causation and cell of origin remain to be discovered.

References