DIAGNOSTIC ELECTRON MICROSCOPY: A HISTORICAL PERSPECTIVE

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The principal discoveries that led to the construction of the transmission electron microscope by Knoll and Ruska in 1931 were those of J.J. Thomson, who demonstrated that cathode rays are negatively charged electrons that could be deflected by an electric field, and of Louis de Broglie, who showed that a moving electron has an associated wavelength which is inversely proportional to its momentum. The optical resolution attainable by transmission electron microscopy (TEM) is much greater than that of a light microscope; it is 0.2 nm for TEM as opposed to 200 nm for a first-class light microscope.

In 1934, Ladislos Marton of Brussels first published a paper that included an electron micrograph of a biological specimen, a section of a *Drosera intermedia* leaf. However, high resolution electron microscopic images of biological cells and tissues were not obtainable until better instruments and better methods of specimen preparations were developed during the decades from 1940 to 1970. These advances included the introduction of osmium tetroxide and glutaraldehyde; methacrylate and epoxy resins; glass and diamond knives; and "electron-dense" lead and uranium salts for staining of TEM grids.

After the first TEM description of a neoplastic cell in a rat by Porter and Thompson in 1947, several isolated reports on the ultrastructural features of human and animal tumors appeared from from 1953 to 1965. During that period, virions also were discovered in neoplastic cells from a variety of animals and in tumor cells from leukemic human patients.

Although ultrastructural analyses of selected specific neoplasms were anecdotally performed in North America & Europe in the early 1960s, no published articles appeared in the general surgical pathology literature on this topic until 1968. At that time, Rosai & Rodriguez described several tumors in which TEM helped to resolve difficult diagnostic interpretations. Subsequent to that article in the *American Journal of Clinical Pathology*, a number of additional papers, reviews, and book chapters expounded on the application of TEM to tumor diagnosis. The first book entirely devoted to that subject was authored by Ghadially in 1980, followed by an illustrated monograph written by Erlandson in 1981. In addition to being an adjunct to the diagnosis of human tumors, electron microscopy has proven useful in the evaluation of various nonneoplastic human diseases such as glomerulonephritides, myopathies, viral infections, and storage disorders. Indeed, the latter conditions now account for the great bulk of cases for which ultrastructural studies are currently obtained.

**CONTRIBUTIONS AND LIMITATIONS OF DIAGNOSTIC ELECTRON MICROSCOPY**

**Contributions**

1. Today, transmission electron microscopy is most often used to help resolve difficult differential diagnoses. For example, is a high grade sarcoma a malignant fibrous histiocytoma, a monophasic synovial sarcoma, a leiomyosarcoma, or a malignant peripheral nerve sheath tumor?

2. Ultrastructural studies can still be useful in the evaluation of tumors with uninterpretable immunohistological findings, or those which for technical reasons are unsuitable for reliable immunohistochemical evaluation.

3. In several selected medical diseases such as myopathies, glomerulonephritides, storage diseases, and others, TEM continues to be the best implement for definitive diagnosis.

**Limitations**

1. Many tumors cannot be examined adequately by TEM because of extensive degenerative changes in them prior to fixation. Improper sampling for ultrastructural study is also a problem.

2. In practical terms, only a small portion of any given tumor can be processed for TEM and therefore sampling bias is a definite issue. A limited amount of time also is available for examining specimens. Diagnostic electron microscopy requires a level of patience and diligence that unfortunately is lacking in many individuals, especially busy surgical pathologists. That is why diagnostic TEM often is relegated to inexperienced pathology residents, PhDs, or technicians.

3. Transmission electron microscopy has been disappointing as a means for establishing the lineage of differentiation for a number of neoplasms, such as alveolar soft part sarcoma, Ewing's sarcoma, epithelioid sarcoma, and synovial sarcoma.
REFERENCES