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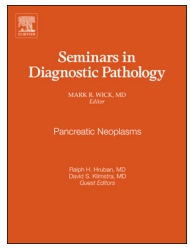

Diagnostic electron microscopy and the influence of Dr. Juan Rosai

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ABSTRACT

Transmission electron microscopy (TEM) was introduced by Ruska and Knoll as a laboratory technique in 1933. Thereafter, several decades passed before the methods required for its optimal implementation were fully developed. Early uses of TEM were in Botany, rather than in Medicine; however, isolated publications did catalog the ultrastructural characteristics of several individual human tumor types. Finally, in 1968, Rosai and Rodriguez authored an important article, introducing the concept that TEM could be used for the differential diagnosis of histologically similar neoplasms. This publication heralded the steadily increasing application of TEM in anatomic pathology over the following decade, including continuing contributions by Dr. Juan Rosai. This brief review summarizes his influence on clinical electron microscopy, and lists some of the lesions for which that procedure is still a useful means of analysis.

A new era of Biology and Medicine began in 1933, with the invention of the electron microscope by Dr. Ernst Ruska—a physicist and Dr. Max Knoll—an electrical engineer.[1] They had the idea to substitute an electron beam for a standard light source in a transmission microscope, and to use electromagnets and electrostatic lenses rather than glass lenses to focus the beam. Variably electron-dense substances (usually uranyl acetate and lead citrate) were utilized to impregnate ("stain") tissue for examination in that system, and a camera was later incorporated into it to obtain a permanent record of the images that were seen. With transmission electron microscopy (TEM), biological structures as small as 50 or 60 nm could be visualized by these early instruments, as compared with a maximum resolution of 1 μm that pertained to even the best light microscopes of the time. The first commercial electron microscope was marketed in 1939, and Ruska was awarded the Nobel Prize in Physics in 1986 for developing this technique.[2]

Unfortunately, TEM was born at a time when the worldwide great depression had taken hold firmly, with all of its economic hardships. That fact, along with its unfamiliarity to scientists and its technically cumbersome nature, markedly limited the implementation of TEM technology. Initial publications on electron microscopy dealt principally with botany, rather than zoology or medicine.[3] Moreover, several years were required to refine and optimize the processes of tissue fixation, embedding, microtomy, staining, and additional specimen preparation. This evolution eventually culminated in the use of glutaraldehyde, epoxy-based media, diamond-knife microtomy, and the mounting of stained sections on copper grids. Another problematic issue was the lack of knowledge on subcellular histology. Normal structure had to be studied and cataloged before pathologic changes could be recognized confidently.

During this period of the "adolescence" of TEM, however, several topical areas were, in fact, informed by that method.

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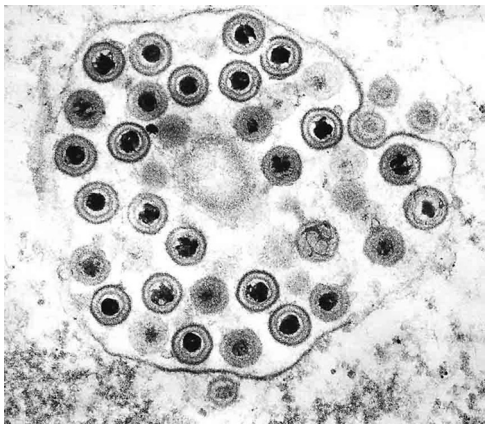

Fig. 1 – This electron micrograph of a neuron shows numerous encapsulated intranuclear viral particles in a case of Herpes simplex encephalitis.

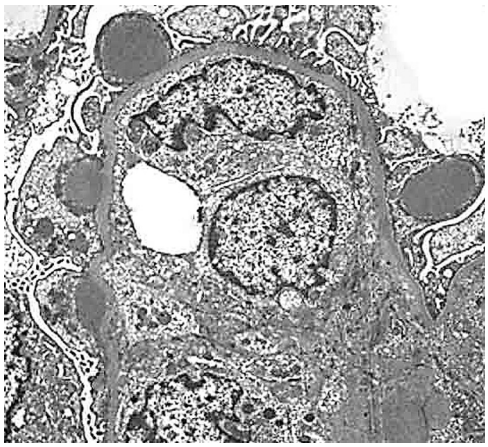

Fig. 2 – Post-infectious glomerulonephritis is shown here, demonstrating the ultrastructural presence of subepithelial glomerular immune deposits.

These encompassed the ultrastructural appearance of several viruses and other microorganisms in plant, animal, and human tissues[4,5] (Fig. 1); the phenotypes of selected medical renal diseases[6] (Fig. 2); fine-structural anatomy of the skin; and the subcellular characteristics of selected human neoplasms. The latter included early studies of human rhabdomyosarcoma,[7] melanoma,[8] neurilemmoma (schwannoma),[9] and prostatic adenocarcinoma,[10] but no systematic effort was made to compare morphologically similar lesions with one another through the mid-1960s. Furthermore, such reports were made in scientific journals with limited readerships, and they did not come to the general attention of most pathologists.

This situation changed dramatically through the efforts of Drs. Juan Rosai and Hector Rodriguez in 1968. At that time, both men were young surgical pathology trainees of Dr. Lauren Ackerman at Washington University in St. Louis, MO. They became interested in new procedures for the segregation of morphologically undifferentiated or indeterminate neoplasms from one another. Choices in that realm were relatively limited, mainly comprising conventional histochemistry, enzyme histochemistry, and tissue-culture studies of viable neoplastic cells that had been removed surgically. The first two of those approaches have the greatest conceptual similarity to TEM, in the sense that they involve the recognition of subcellular chemical moieties or structures that distinguish between cell types and lineages. However, that fact had not really been appreciated or exploited before in a methodical way. Rosai and Rodriguez reasoned that just as histochemical evidence of mucin production could be used to separate adenocarcinomas from other morphologically similar malignant tumors, the presence of certain fine-structural findings might similarly prove to be discriminatory. That premise proved to be true, based on the results of a study that the authors published in the American Journal of Clinical Pathology (AJCP).[11] They had selected a group of neoplasms with uncertain identity at a histological level, but which demonstrated reproducible and obvious differences ultrastructurally. For example, just as in

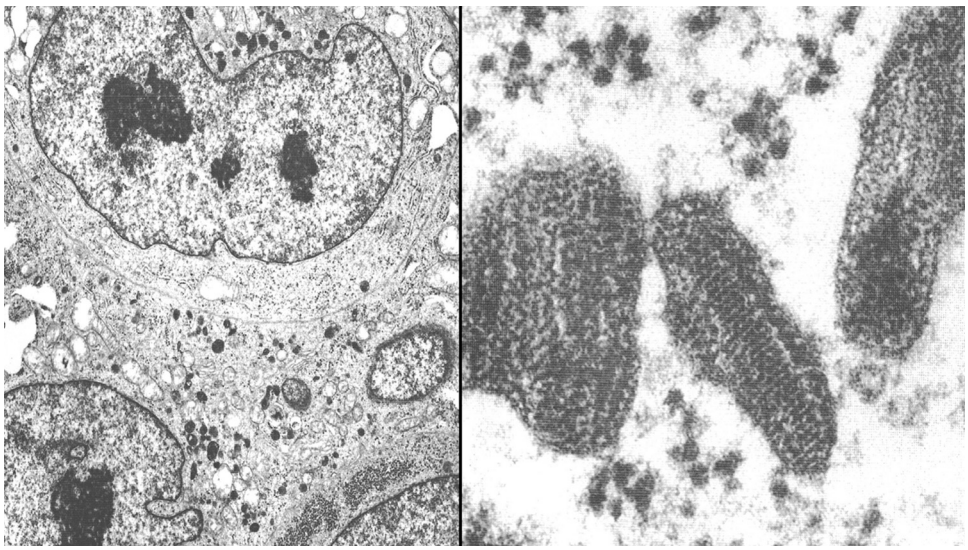

Fig. 3 – Electron microscopy of amelanotic melanoma shows polygonal cells joined by sparse intercellular junctional complexes (left) and containing cytoplasmic premelanosomes (right).