The history of diagnostic cytology is like a winding road with many obstacles, but to the attentive traveler—the historian—brightly illuminated directional signs and familiar names are visible in the distance. Until the 19th century, microscopy was not respected in medicine. Such giants in pathology as the Italian Morgagni (1682–1771), the British Baillie (1761–1823), and the French Bichat (1771–1802), did not appreciate the utility of the microscope.

There were four great technical advances that gave impetus to microscopic examination of tumor cells in smear preparations. It all began in the 1830s with imprint smears and continued with sporadic microscopic examination of sediments from body fluids. And finally, in the 1920s, aspiration and exfoliative cytology were introduced.

Johannes Müller (1801–1858), a pathologist in Berlin (Fig. 1), was the first, in 1836, to show cancer cells as they appeared in the microscope on scrapings from the cut surface of surgically-excised tumors. He illustrated, among other things, cells of mammary carcinoma and osteosarcoma [1]. In 1843, cancer cells were shown on scrapings from a uterine cervical cancer [2] and cytologic preparations were made from a fistulous parotid tumor believed to be malignant [3]. A year later, colored prints of tumor cells of breast carcinoma, sarcoma of the mandible, and soft tissue sarcomas of the leg were published [4]. In 1846, the same author described and illustrated cancer cells in blood-stained sputum of a patient with lung cancer and in the vomitus of another patient who had gastric cancer [5].

Lebert (1813–1878), a French pathologist, collected specimens for cytologic examination from effusions, tracheobronchial secretion, and urine. He prepared innumerable imprint smears from surgical specimens, including tumors and non-neoplastic lesions. His cytology atlas, published in 1845, contains more than 250 cytologic illustrations. The pictures were taken through the microscope by the newly-invented Deguerre technique [6].

Paget (1814–1879) prepared smears from needle aspirate of a breast carcinoma in 1853 [7]. Malignant cells were diagnosed in urine in 1856 [8] and in 1869 cancer cells were recovered from material passed by the urethra [9]. By the 1890s, diagnosis of bladder tumors by microscopic examination of urine had become a routine procedure [10]. Cytologic examination of sputum was soon introduced as routine laboratory procedure [11] and microscopic examination of ascitic fluid was employed for diagnosis of peritoneal carcinomatosis [12]. Malignant cells were recovered from cerebrospinal fluid in 1904 [13] and shortly thereafter gastric washing was introduced [14].

The 1920s were momentous years in diagnostic cytology. The first monograph of clinical cytology was published in Spain [15]. James Ewing (1866–1943) introduced aspiration cytology in New York City [16]; and Aurel Babes (1886–1961), of Rumania, and George Papanicolaou (1883–1962), of New York City, published papers on detection of uterine cervical cancers by examination of vaginal smears [17,18]. The medical profession largely ignored Babes's and Papanicolaou's discoveries for nearly two decades, but in the interim, in the 1930s, cytologic examination was extended to all body sites and all possible specimens [19–26]. Above all, Ewing and his associates [27–29] popularized needle aspiration cytology and extended its use for deep and superficial lesions (Fig. 2).

It is of historical interest that while aspiration cytology was used daily as a diagnostic
In the pathology laboratory of James Ewing at the southwest corner of 68 Street and York Avenue, at the Memorial Hospital for Cancer and Allied Diseases, across the street, at the northeast corner of 68 Street and York Avenue, at the New York Hospital Cornell Medical School. George Papanicolaou and his associates published, in 1941, their epoch-making paper on the diagnostic value of vaginal smears in carcinoma of the uterus [30]. Papanicolaou with his associates, trainees, and disciples popularized cytology and extended the original technique for collection of specimens and staining of smears to all body sites [31–40]. The first cytology monographs began to appear in the late 1940s [41–42].

In the 1950s, Papanicolaou himself [43] and others [44–47] published substantial texts on cytologic diagnosis of uterine and other cancers (Fig. 3). Simultaneously, national and international cytology associations were formed and a specialty journal, Acta Cytologica, was inaugurated. Accurate cytologic diagnosis of upper and lower gastrointestinal cancers was made feasible by introduction of improved lavage and balloon techniques [48–50]. Smears were prepared from nipple secretions [51], thyroid aspirates [52], and new cytology terms such as koilocytotic atypia [53] were introduced.

In 1961, Leopold Koss (Fig. 4), a pathologist at the Memorial Hospital for Cancer and Allied Diseases, a student of Papanicolaou and a disciple of Ewing, published the first comprehensive textbook on cytopathology [54]. In this book, Koss presented a concise review of state-of-the-art exfoliative and aspiration cytology with consideration of the histopathologic basis of various lesions. The book became the standard text in cytology and went through five editions during ensuing years.

In the 1960s, cytology became accepted as a new specialty in pathology. During the next two decades, cytology branched out to all fields in medicine [55–57]. Cytology of even the most uncommon tumors became familiar to cytologists [58–62]. New and improved imaging techniques in radiology permitted rapid advances in aspiration cytology. Hitherto untouched, deeply situated organs such as the pancreas became easy targets for the aspirators [63–69]. The first monograph on aspiration cytology was published in 1974 by a Swedish hematologist–cytologist [70] and a guidebook on aspiration cytology was published in the United States in 1981 [71].

After an arduous 150 years, with many stops and detours, cytologic examinations in the last 25 years have become indispensable routine laboratory procedures and aspiration and exfoliative cytology has gained recognition as a subspecialty of pathology.

---

**Fig. 1.**

Johannes Müller (1801–1858) made the first smears from tumors in 1838 [1].

**Fig. 2.**


**Fig. 3.**

George Papanicolaou (1883–1962). U.S. postage stamps of 1978 honor the world-renowned cytologist for his development of the “Pap. smear” for early detection of cancer. The two stamps are shown on a commemorative envelope printed by the Memorial Sloan-Kettering Cancer Center in New York City.
References

4. Walsh WH. Anatomy, Physiology, Pathology and Treatment of Cancer. Ticknor, Boston, 1844. »Google Scholar
28. Ewing J. Causation, Diagnosis and Treatment of Cancer. Williams and Wilkins, Baltimore, 1931. »Google Scholar
The diagnostic algorithms for evaluation of cystic and solid lesions of the liver are provided in Boxes 45.6 and 45.7, respectively. Evaluate ancillary studies. The initial cytomorphologic impression is often crucial because the small amount of material may limit the utility of immunohistochemical and other ancillary tests.