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MEDICAL HISTORY

A Brief History of Breast Cancer

Part II - Evolution of surgical pathology

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ريتو لكتاكيا و روشان شينوي

The origins of pathology (Greek, *pathologia* = 'study of emotions or suffering') could perhaps date back to ancient physicians struggling through observations and philosophy to unravel the mysteries of the human body and its afflictions. While the recordings of the Egyptians (3,500–2,000 B.C.) revealed through the Edwin Smith Papyrus, the Mesopotamians (Code of Hammurabi, 2200 B.C.) and the Greek civilisation (Hippocrates 460–370 B.C.) attributed deformity and destruction to demonical, deitical or humoral influences,[1,2,3] it was only during the golden Islamic age from the 8th century and the Renaissance period of European history that the earliest seeds of scientific pathological practice were sown. Surgery, until the last century the only modality to treat breast cancer, predated the evolution of 'surgical' pathology by millennia narrated in part I of this article.[4] Technological advancement combined with insightful understanding of pathogenesis made pathology the focal point of oncological practice only in the 19th century. The science of breast cancer benefited from its emergence.

Physicians, Anatomists and Surgeons: *Forerunners of macroscopic pathology*

The philosopher-physicians Hippocrates and Galen, contemplating the origin of disease, were perhaps the first to attempt an understanding of 'pathogenesis' (the aetiology and mechanisms of disease causation). Undeniably, a more vital and demonstrable direction emerged in the performance of autopsies as far back as the 12th century by Arabian physicians Avenzoar (1090–1162)[5,6] and Ibn Al-Nafis (1213–1288),[7] followed by Antonio Benivieni (Florence, 15th century), Giovanni Morgagni (Italy, early 18th century) and Karl von Rokitansky (Vienna, mid-19th century). Many of these physicians had the foresight to perform and record their autopsy findings. Von Rokitansky is believed to have performed over 30,000 autopsies in his lifetime. This accumulation of knowledge, initially aimed at teaching and research, subsequently generated a wealth of information on which surgeons could draw when dealing with live patients.[8]

The practice of medicine witnessed an enviable intertwining between disciplines—demonstrated best by surgeons beginning their careers as anatomists. American surgeons in the 19th century, in turn initiated 'surgical' pathology and the role of the surgical pathologist. Their astounding clinical and intra-operative appraisals, guiding the steps of a surgical procedure, laid the foundation for the development of pathology as an independent specialty in later years.[9,10] Many of them trained under 19th century physicians of repute in Germany and went on to lay the foundations of medicine and pathology in their own country.

The English anatomist and surgeon, Sir Astley Paston Cooper (1768–1841), brought breast disease to the forefront through his prolific publications on a host of organs including the breast (*Illustrations of Diseases of the Breast*, 1829; *Anatomy of the Breast*, 1840). Modern day oncoplastic breast surgery owes its principles of segmental resection to Cooper's incisive exploration of breast anatomy. He lent his name to the eponymous Cooper's ligaments (suspensory ligaments of the breast), Cooper's disease (cystic disease of the breast) and Cooper's neuralgia (neuralgia of the breast).[11]

John Collins Warren (1778–1856) of the Massachusetts General Hospital (MGH), Boston, and Joseph Colt Bloodgood (1867–1935) of Johns Hopkins Hospital, Baltimore, surgical pioneers of renown, drew the pathologist to the surgeon's theatre of operations

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with the promise that "the combination of energies which accomplishes most in surgical progress is that contained by the cooperation of the laboratory investigator with the surgeon of clinical experience".[12] Championing the significance of macroscopic appearance to guide surgical options they paved the way for rapid diagnosis by the intra-operative frozen section. Warren, defying contemporary practice, also advocated the pre-surgical biopsy of breast tumours. His intense preoccupation with microscopy is exemplified in the extensive illustrations of breast tumours in a book published in 1895.[13]

Across the Atlantic, Sir George Lenthal Cheatle (1865–1951), a British surgeon, and his American colleague Dr. Max Cutler, not only operated and studied thin slices of breast tissue, but documented their findings for posterity in 1931, in what is recognised as the first modern textbook of mammary pathology, *Tumors of the Breast, Their Pathology, Symptoms, Diagnosis and Treatment*.[12] Their prodigious contributions to pathogenesis included postulating the origin of breast cancer from mammary epithelial cells and changing the understanding of papillary and biphasic tumours.

Technological Renaissance and the Microscopic Eye

The emergence of microscopy, beginning with the chiselling of lenses, was transformed into a new world of disease visualisation by the early, simple (Antonie Van Leeuwenhoek, 1632–1723) and compound (Robert Hooke, 1635–1703) microscopes.[14]

The 19th century German pioneer Johannes Müller (1801–1858) laid the foundation for the understanding of the cellular character of new growths in his work *On the fine structure and form of morbid tumors* in 1838, leaning heavily on the clinical differences between benign and malignant tumours. Schwann, Henle and Virchow, themselves historical figures of note, were his protégés; Henle authored the *Handbook of Rational Pathology* (1846–1853) used extensively by students of the time.[15]

The success of the collaboration between the science of optics and human biology is best exemplified in Virchow's (1821–1902) medical epic *Die Cellularpathologie*, published in 1871 nearly 150 years since the advent of microscopy. The brave new world of cellular pathology heralded by the 'Father of Pathology' was to unravel disease as never before. Virchow's now famous aphorism *omnis cellula e cellula* (every cell stems from another cell) in 1855 resounds through medical history right up to the modern era of stem cell technology.[16] His legendary contributions to medicine could be considered the launching pad for the post-Virchow era of diagnostic pathology as we know it today. From microscopic diagnosis to photomicrography (illustrating disease patterns to peers through publications or presentations) was just another short step.

While microscopy offered magnification of tissues, it was the innovations in tissue processing (fixation and embedding), microtomy (section-cutting) and finally the fine art of staining that allowed the pathologist's eye to analyse the myriad complex tissue patterns that define disease.[17]

Breast Cancer and the Pathologist: *Biopsy and cytology take a leap forward*

Once microscopy became a part of disease evaluation, the time was ripe for establishing departments of pathology in institutions, removed from the 'gross' pathology observations and recordings by surgeons. In 1854, Dr. Barnard Jackson became the first professor of Morbid Anatomy at the Harvard Medical School (and the first in the USA). However, he was still of the old school—relying exclusively on macroscopy. The microscope was pressed into service in 1847 through the efforts of his friend and colleague Oliver Wendell Holmes.[13]

J. Collins Warren (1842–1927),[18] grandson of John Collins Warren (co-founder of MGH) drew on his European training in surgery and pathology and pioneered the use of needle biopsy in the diagnosis of breast cancer and the frozen section (the latter technique has also been credited to the Johns Hopkins gynaecologist-pathologist, Thomas S. Cullen).[19] The procedure revolutionised decision-making at the operating table.

Notable luminaries in the saga of the various forms of breast neoplasia in the 20th century include New York pathologists, Arthur Purdy Stout (1885–1967) and Cushman D. Haagensen (Columbia University 1933–1975) who elucidated the nature of papillary lesions and lobular neoplasia.[20] At the Memorial Hospital, New York, Fred Stewart and Frank Foote's lifetime explorations into breast disease were documented through their classification of tumours.[21] In the latter half of the 20th century, John G. Azzopardi (1929–2013) at the University of London stood as a giant in breast pathology. His authoritative masterpiece *Problems in Breast Pathology* has served as a bible of breast pathology.[22]

Fine-needle aspiration cytology provided a simple, relatively non-invasive tool for the rapid diagnosis of breast lumps with high reliability. Early reports of its usage in the 20th century originated from the Memorial Hospital, New York, in the 1930s.[23] However, in the USA its subsequent practice became erratic, partly due to the prevailing litigious environment in healthcare. Later in the century, Scandinavian workers anchored its popularity.[24] Its usefulness has remained steady across the world as part of the triple assessment of a breast lump; publications on its use for breast disease rank it first in frequency in developing and second in developed countries.[25]

New Frontiers of Pathobiology of Breast Cancer: *Prediction and prognosis*

Conventionally, consensus-based morphological classifications (World Health Organization classification of breast tumours),[26] grading systems illustrating tumour differentiation,[27] and the tumour-nodes-metastasis (TNM) staging[30] have been the bedrock for assessing tumour aggressiveness.

Pathobiologists started exploring cell biology to identify new pathways of tumourigenesis leading to new therapeutic options. The hormone-dependence of breast cancer, long suspected through clinical observation became a scientific fact through Jensen's identification of oestrogen and progesterone receptors (ER, PR) on breast cancer cells in 1967.[29] Today, the immunohistochemical demonstration of ER/PR and the epidermal growth factor receptor (Her2/neu) on core biopsies has been standardised through well-established protocols.[30] The modern-day pathologist is, thus, at the heart of therapeutic decision-making and shares the responsibility of rendering information on prognostication and prediction.

In a seminal article in *Nature* in 2000, Perou *et al*. created 'molecular portraits' of breast cancer by analysing 65 surgical specimens using complementary DNA microarrays of 8,102 genes.[31] Intense exploration of this information resulted in high throughput gene expression profiling technology-driven assays (Oncotype Dx, MammaPrint) rapidly transiting from the bench to the bedside and holding promise for 'personalised' medicine.[32] Industry-driven and automated, their expanding role is being watched carefully; the future may see some of these incorporated into practice, while others will fall by the wayside. Alternatively, a marriage between pathological and molecular inputs may provide a unified diagnostic tool bridging efficacy, availability and affordability for global practice.[33]

Lessons from the Evolution of Surgical Pathology in Breast Cancer

The history of the pathological diagnosis of breast cancer is a fine example of the emergence of a discipline driven by clinical observations and curiosity and fuelled by technological advances. The breaking point in this journey came with the advent of microscopy that solidified forever the superiority of microscopic diagnosis. It is also an excellent example of the achievements possible with contributions from physics (optics), chemistry and natural sciences (stains) and engineering (microscopes, microtomes and automation). In the last half century, immunology and genetics have enabled the refinement of diagnosis, a better understanding of tumour biology and have brought in targeted therapy. Genetic inputs will still need to be tempered and teased into context by the tenacity of the pathologist's eyeballing skills, backed by the knowledge of the complexities of tumour biology. These remarkable contributions allow breast preservation and even a cure for a once incurable disease.

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