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Endocrine pathology: past, present and future

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Summary

Endocrine pathology is the subspecialty of diagnostic pathology which deals with the diagnosis and characterisation of neoplastic and non-neoplastic diseases of the endocrine system. This relatively young subspecialty was initially focused mainly on thyroid and parathyroid pathology, with some participants also involved in studies of the pituitary, the endocrine pancreas, and the adrenal glands. However, the endocrine system involves much more than these traditional endocrine organs and the discipline has grown to encompass lesions of the dispersed neuroendocrine cells, including neuroendocrine tumours (NETs) of the lungs, gastrointestinal tract, thymus, breast and prostate, as well as paraganglia throughout the body, not just in the adrenals. Indeed, the production of hormones is the hallmark of the endocrine system, and some aspects of gynecological/testicular, bone and liver pathology also fall into the realm of this specialty. Many of the lesions that are the focus of this discipline are increasing in incidence and their pathology is becoming more complex with increased understanding of molecular pathology and a high incidence of familial disease. The future of endocrine pathology will demand a depth of understanding of structure, function, prognosis and prediction as pathologists play a key role in the multidisciplinary care team of patients with endocrine diseases. It is anticipated that new technologies will allow increased subspecialisation in pathology and growth of this important area of expertise.

Key words: Endocrine pathology; history; biomarkers; genetics; epidemiology.

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INTRODUCTION

The history of surgical pathology, like many other disciplines in medicine, is one of evolution based on demand for expertise. Pathology as a science originated in the investigations of clinicians whose curiosity drove them to better understand the diseases they saw and tried to treat. In endocrinology, biochemistry was the basis for measuring changes in the hormonal environment. As surgical pathology grew in importance, the structural changes that reflected functional alterations started to emerge. Advances in surgery and increasing experience with structure-function correlations have allowed this field to blossom into a significant area of pathology subspecialisation.

This review will provide some historical perspectives, describe the scope of endocrine pathology in the 21st century and offer a vision of the challenges and opportunities that face the discipline.

HISTORICAL PERSPECTIVES

Endocrine pathology plays a role in history as far back as biblical times. The story of David and Goliath provides an accurate description of gigantism, acromegaly, visual field loss due to a large pituitary tumour, and apoplexy induced by trauma. The fragility of Goliath's bone raises the possibility of multiple endocrine neoplasia type 1 with hyperparathyroidism.

In ancient Egypt, the Pharaoh Akhenaton likely had a pituitary tumour. He may have had acromegaly and had features of hypopituitarism; however, the pituitary was not included in the mummy because it was discarded during the embalming process when the brain was removed through the nose of the deceased.

The concept of hormones emerged as far back as 200 BC when the Chinese recognised that extracts of human urine provided medicinal benefits. Galen (129–201AD) described the pituitary; he thought that it served as the site of drainage of phlegm from the brain to the nose and throat.

In 1649, Descartes proposed that the brain is responsible for integrating the functions of the mind and body.[1] The relationship between the brain and its targets was further clarified by Morgagni (1733), Soemmering (1792) and Meckel (1802) who described absence of the adrenals in anencephaly, and Zander (1890) again advocated for a connection between the brain and the adrenal glands.[2] In the 1800s, Flajani (1802),[3] Testa (1810),[4] Parry (1786),[5] Graves (1835),[6] and von Basedow (1840),[7] described goitre, exophthalmos, and symptoms of hyperthyroidism. The year 1849 saw three important discoveries: Arnold Berthold showed that castrated cockerels do not develop combs and wattles or exhibit overtly male behaviour, but replacement of testes back into the abdominal cavity of the same bird or another castrated bird resulted in normal behavioural and morphological development.[8] Claude Bernard described 'le piqûre diabetique', injury to the floor of the fourth ventricle that caused excessive urination.[9] Thomas Addison described the clinical features of adrenal cortical insufficiency that was subsequently published in 1855.[10]

The description of acromegaly by Pierre Marie in 1886[11] was followed by Minkowski's association of that clinical

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disorder with a pituitary tumour in 1887.[12] In 1889, Brown-Séquard showed that extracts of animal testes enhanced physical strength, improved intellectual capacity and increased sexual potency.[13] The same year, von Mering and Minkowski showed that removal of the pancreas lead to an increase in blood sugar and diabetes mellitus.[14] In 1867, while working in Rudolf Virchow's laboratory in Berlin, Langerhans discovered previously unrecognised clusters of pancreatic cells within sheets of acinar cells.[15] Laguesse named these 'islets of Langerhans' and postulated that they produce an internal secretion,[16] and it was the nomenclature of islets that ultimately led to the terminology 'insulin' by Banting and Best in 1922.[17]

The year 1902 led to the definition of the field of endocrinology. Bayliss and Starling discovered 'secretin' that stimulated pancreatic secretion and was produced in the duodenum and jejunum.[18] They defined a 'hormone' as a chemical produced by an organ, released (in small amounts) into the blood to be transported to a distant organ to exert its function.

The pathology of endocrine tumours took a step forward in 1907 when Siegfried Oberndorfer described 'karzinoide' ('carcinoma-like') tumours of ileum.[19] While he initially classified them as benign or indolent tumours, in 1929 he amended his classification to recognise their metastatic potential. He did not associate these tumours with their endocrine activity; in 1897 Kulchitsky had described enteroendocrine cells but was unaware of their function[20] and the association with serotonin was not established until 1953 by Lembeck.[21]

The 20th century saw tremendous progress. Simmonds in 1914 described pituitary cachexia (hypopituitarism),[22] Cushing (1912, 1932) described adrenal hyperfunction, the syndrome that now bears his name, and pituitary-dependent adrenal excess, the disease that is eponymic.[23] Banting and Best purified insulin and reported its first successful use in 1922.[17] In 1937, Sheehan described postpartum hypopituitarism.[24] Harris identified multiple hormones of the anterior pituitary and their regulation by the hypothalamus in 1948.[25] Sanger sequenced insulin in 1953.[26] In 1954, du Vignaud was awarded the Nobel Prize in Chemistry for the first synthesis of a polypeptide hormone; in 1977, the Nobel Prize in Physiology or Medicine was dedicated to endocrinology, half going to Rosalyn Yallow for the development of radioimmunoassays of peptide hormones, and the other half shared by Roger Guillemin and Andrew Schally for the isolation and characterisation of hypothalamic-pituitary hormones.

The first textbook of endocrine pathology was published in 1968 by Bloodworth. This book was followed in 1990 by a flourish of activity including the formation of the The Endocrine Pathology Society as a Companion Society of the United States and Canadian Academy of Pathology, the initiation of a journal *Endocrine Pathology*,[27] and the publication of a textbook, *Functional Endocrine Pathology*. Today there are many textbooks in this field, the journal continues to thrive, and Societies have been formed in many countries around the world.

THE SCOPE OF ENDOCRINE PATHOLOGY

Endocrine pathology is the study of diseases that affect the endocrine system, a complex network of hormone-producing cells and organs that is dispersed throughout the body. Endocrine tissues are grouped into three major categories.

The largest group of endocrine cells forms the neuroendocrine system; the cells that comprise this system produce peptide hormones, many of which also can function as neurotransmitters. They signal through mechanisms that also resemble neuronal signalling. The difference between neurotransmission and endocrine transmission is based on the proximity between the site of discharge and the target cell; neurons release their product at the synapse where it travels to an adjacent cell, whereas neuroendocrine cells typically release their products into the bloodstream, and the target may be distant in other parts of the body, as in classical endocrinology, or nearby, a phenomenon that came to be known as paracrine signalling.

These cells have been the subject of intense study for many years. An important concept was their ability to take up amines for peptide synthesis, a characteristic that gave rise to the terminology 'amine precursor uptake and decarboxylation' (APUD) for this system.[28] The origin of these cells in the neuroectoderm was a fundamental principle of this theory that led to controversy and ultimately discredited its proponents, despite the minimal importance of this aspect. It is now widely recognised that some neuroendocrine cells are epithelial and of endodermal origin; they can form glands, for example the pituitary, they may form small structures within other tissues, as the islets of Langerhans, or they may be dispersed in other tissues, such as endocrine cells of the thymus, lung, and gut. Other neuroendocrine cells represent modified neurons that are of neuroectodermal origin and have no epithelial features; these paraganglia are distributed in the sympathetic and parasympathetic systems and include the adrenal medulla as the largest glandular structure. Thyroid parafollicular C cells and parathyroid glands may represent epithelial neuroendocrine cells of neuroectodermal derivation, emphasising the lack of relevance of embryological derivation. Despite the differences in origin, they all have common structural and functional characteristics. They have well-developed rough endoplasmic reticulum for peptide synthesis, large Golgi complexes for packaging of their hormonal products, and numerous secretory granules that store and transport hormones to the cell surface for release by exocytosis (Fig. 1). They all can express neuron specific enolase, synaptophysin, secretogranins and chromogranins (Fig. 2a) as well as enzymes involved in peptide hormone synthesis and processing. Antibodies are available to many of the biomarkers of cell differentiation and to a large number of the transcription factors and peptide hormones[29] that define each cell type (Fig. 2b–e).

A second class of endocrine cells encompasses the steroid hormone secreting cells. These include the adrenal cortex, and steroidogenic cells of the testes and ovaries. Unlike other endocrine cells, these arise from the mesoderm during embryogenesis. These cells take up cholesterol to produce fat-soluble hormones including glucocorticoids, mineralocorticoids, oestrogens, progestogens, testosterone and its precursors. These cells are characterised by well-developed smooth endoplasmic reticulum and large mitochondria that have prominent and unusual tubulovesicular cristae (Fig. 3), a feature of all steroid hormone producing cells with the single exception of those comprising the zona glomerulosa of the adrenal cortex. They are capable of metabolising cholesterol through expression of cholesterol side-chain cleavage (SCC)

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