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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.

## 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

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)
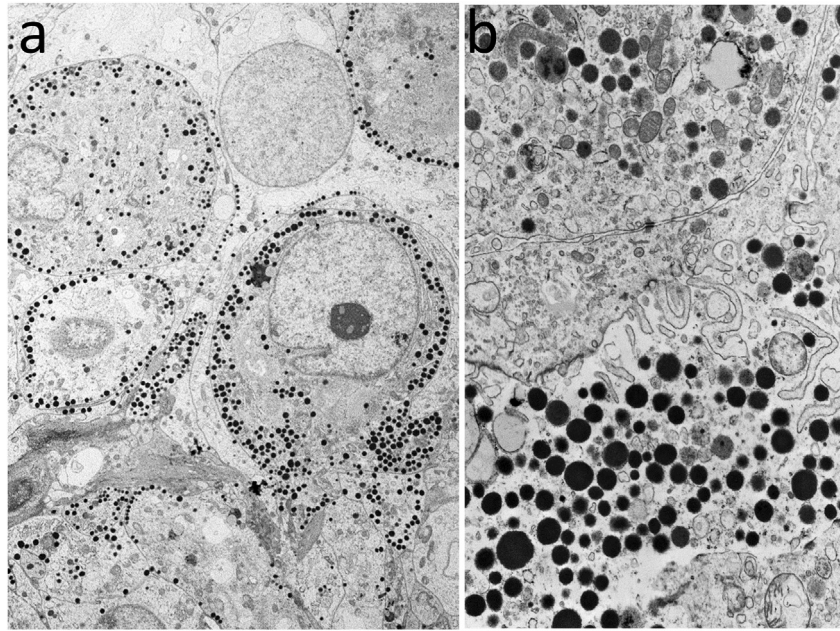
**Fig. 1** Ultrastructural features of peptide hormone-secreting neuroendocrine cells. (a) The cells have well defined cell borders. Their cytoplasm is filled with abundant rough endoplasmic reticulum, prominent Golgi complexes and numerous membrane-bound secretory granules. (b) The secretory granules of the various cell types differ; in this electron micrograph, the top cell has secretory granules that have flocculent contents whereas those of the bottom cell have electron-dense secretory material.
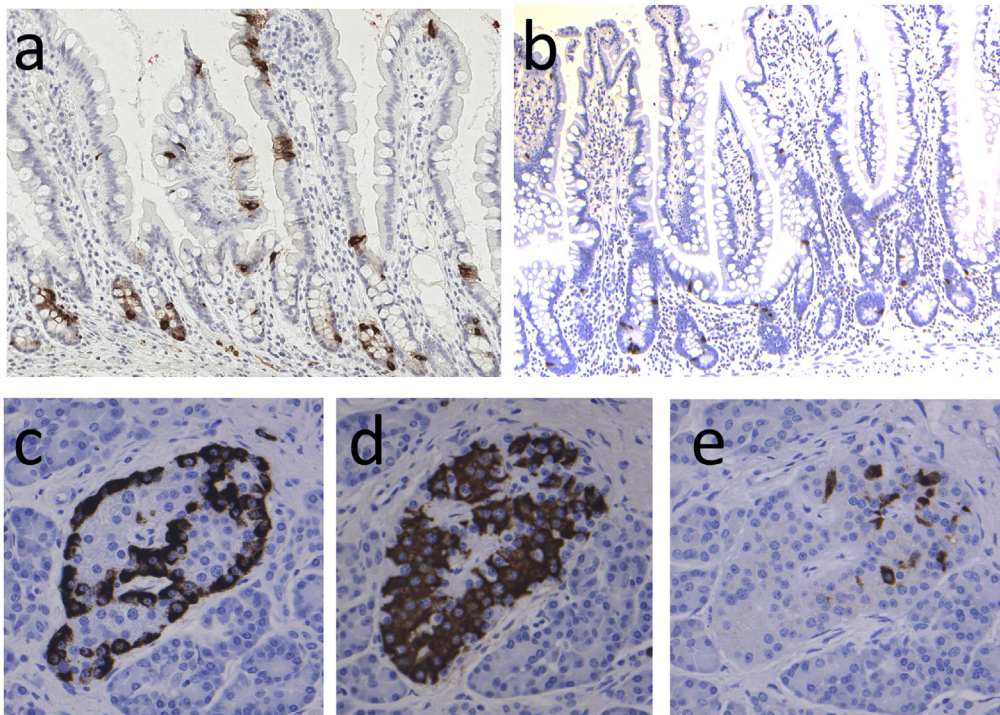


**Fig. 2** Immunohistochemistry of peptide hormone-secreting neuroendocrine cells. (a) The small intestinal epithelium contains numerous endocrine cells that stain for chromogranin. (b) A subset of the chromogranin-positive cells express serotonin. (c) An islet of neuroendocrine cells in the pancreas has cells that express glucagon, known as A or α cells, at the periphery of the trabeculae that comprise the islet. (d) The central mass of the islet trabeculae is composed of insulin-producing B or β cells. (e) Scattered randomly between the glucagon- and insulin-producing cells are the D or δ cells that produce somatostatin.

enzyme and metabolism to the various progestogens, androgens, oestrogens, glucocorticoids and mineralocorticoids through specific expression of 3-beta-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase, 21-hydroxylase, 17,20 lyase, 11β-hydroxylase, aldosterone synthase, aromatase and 5α-reductase. Steroid hormones are fat-soluble and therefore cannot be localised in formal fixed, paraffin embedded tissue, but these cells can be characterised based on their common expression of a transcription factor, steroidogenic factor-1 (SF-1) (Fig. 4), the frequent expression of alpha-inhibin, and the expression of the various enzymes that can be used to determine functional status of these cells.
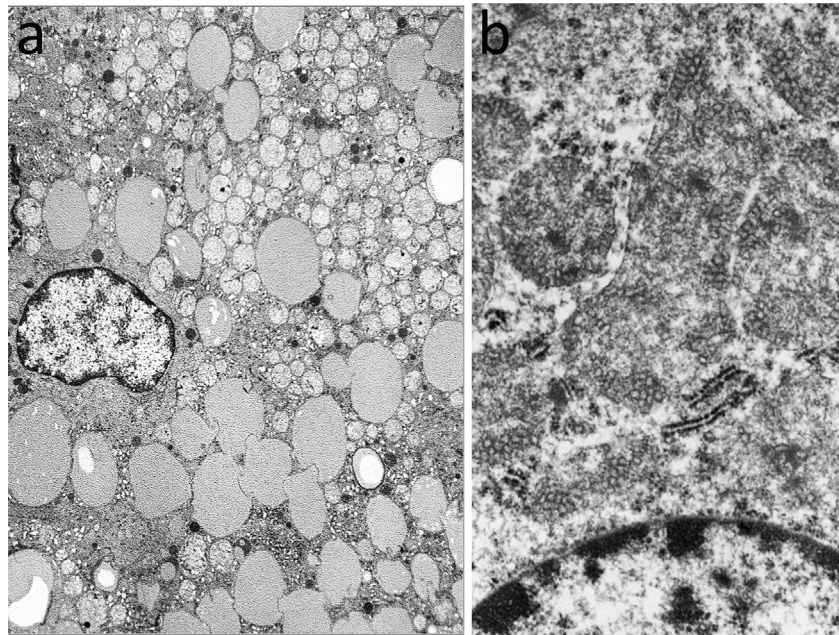
**Fig. 3** Ultrastructural features of steroid hormone-producing cells. (a) Cells that produce steroid hormones are characterised by an abundance of cytoplasmic smooth endoplasmic reticulum, large lipid droplets, and numerous mitochondria. (b) The mitochondria of steroid hormone-producing cells have a characteristic morphology: they have prominent tubulo-vesicular cristae. The exception to this feature is the cells responsible for mineralocorticoid production in the adrenal zona glomerulosa that have conventional plate-like cristae (not shown).
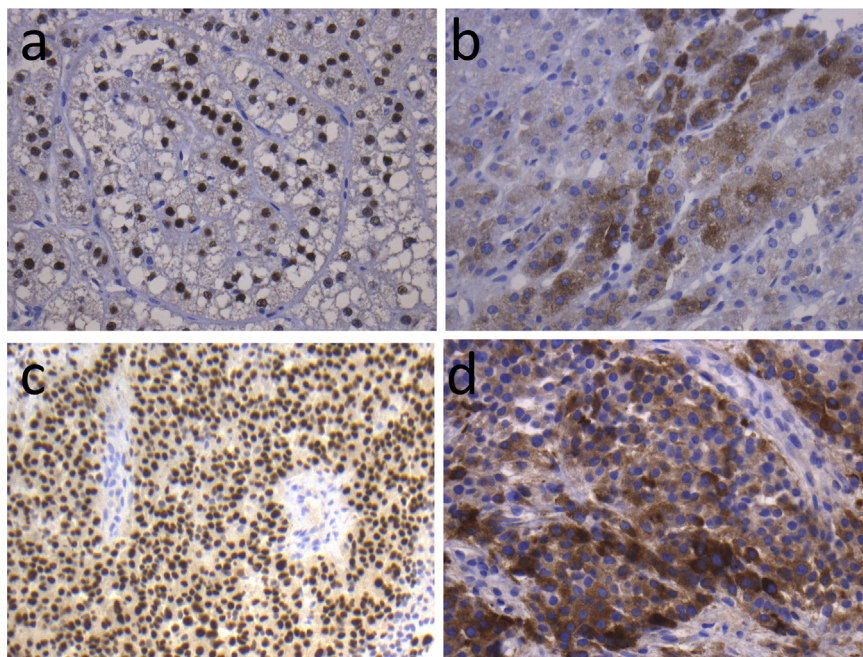


**Fig. 4** Immunohistochemistry of steroid hormone-producing cells. (a) Steroid hormone-producing cells express nuclear steroidogenic factor-1 (SF-1) as shown in this photomicrograph of normal adrenal cortex. (b) They also express inhibin in the cytoplasm with variable intensity, as seen in this normal adrenal cortex. (c) Tumours of steroid hormone-producing cells can be identified based on the nuclear expression of SF-1. (d) In addition to SF-1, tumours of steroid hormone-secreting cells express cytoplasmic inhibin.

The smallest family of endocrine cells is the most common site of pathology. Thyroid follicular epithelium is a unique epithelial cell type of endodermal origin that synthesises and secretes thyroid hormones. These cells are characterised by the formation of tight junctions that are required for the critical follicular structures that are the site of thyroglobulin storage and the prominent microvilli that are necessary for reabsorption of that substance for thyroid hormone synthesis (Fig. 5). They express the transcription factors PAX-8, TTF-1

(Fig. 6a), and TTF-2 (FoxE1) that are required for follicular cell differentiation including expression of the thyroglobulin (Fig. 6b) and thyroid peroxidase genes, the sodium iodide symporter that is required for iodine uptake, and pendrin that acts at the apical aspect for chloride/iodide transport.

The recognition of endocrine pathology as a discipline has faced many hurdles because of this huge scope. As subspecialisation in pathology emerged, many experts and departments felt that distribution of cases and expertise should
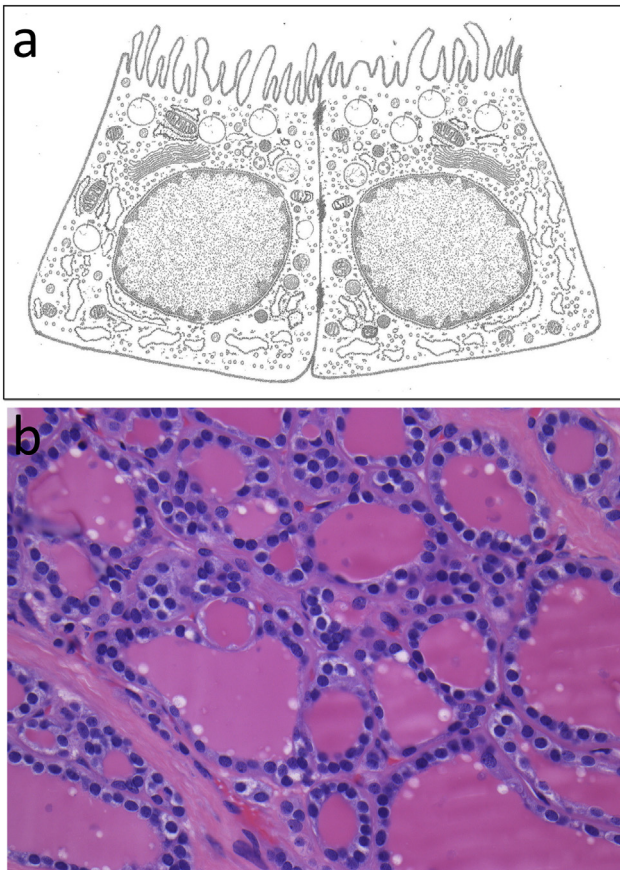
Fig. 5 The structural features of thyroid follicular epithelial cells. (a) The ultrastructure of thyroid follicular epithelium is characterised by distinct polarity of cells with basal nuclei, intercellular junctions and luminal microvilli that secrete and resorb colloid from the follicular lumen. The rough endoplasmic reticulum is abundant and Golgi complexes are well-formed. (b) The follicular architecture is illustrated in this normal thyroid stained with haematoxylin and eosin.

neck pathology, adrenals were the territory of genitourinary pathology, and NETs belonged to gastrointestinal or lung pathology.

The fundamental problem with this approach is that endocrine pathology has several dimensions that are unique and bring together all the various components under one unifying umbrella. Unlike many other aspects of surgical pathology, the investigations are not only about structure, but rather include the critical component of function.[30] The hormonal activity of endocrine pathologies is an important diagnostic and prognostic feature that must be assessed for clinicopathological correlations. In many cases, the functional differences dictate distinct strategies for clinical surveillance and therapeutic decisions. Add to this the complexity of ectopic hormone production wherein any NET can secrete the hormonal product of another endocrine site, and one begins to understand the need for a deeper understanding of the principles of endocrinology. Another critical distinction is the importance of the genetic basis of endocrine diseases. Since Erdheim described multiple endocrine neoplasia (MEN) type 1 in 1903,[31] and this became recognised as an autosomal dominant trait by Wermer in 1954,[32] additional familial endocrine syndromes have emerged and now include many syndromes with multiple genetic alterations that provide a new dimension to the diagnosis of almost every endocrine tumour (Table 1).[33] Similarly, endocrine autoimmune diseases have become recognised as familial disorders.[34]

## CHALLENGES AND OPPORTUNITIES: TRENDS IN ENDOCRINE PATHOLOGY

The incidence of endocrine diseases is increasing. Other cancers associated with lifestyle causation are seeing decreases due to prevention; in some cases, early detection is reducing the burden of cancer. However cancer statistics have shown increases in thyroid cancer,[35,36] NETs are also increasing,[37] and pituitary tumours have gone from rare disorders to common lesions that have a prevalence of approximately 1 per 1000 population.[38,39]

As the incidence increases, so does the complexity of the pathology of these lesions. New tools have clarified the molecular alterations underlying endocrine cancers.[40−42] This has led to new concepts in thyroid tumour classification[43−45]

be determined by the anatomical location of pathology. This was logical in some respects, because the radiologists who image these lesions and the surgeons who operate on the patients were experts in the anatomical regions that harboured the pathology. Thus, pituitary fell into the territory of neuropathologists, thyroid and parathyroid were part of head and
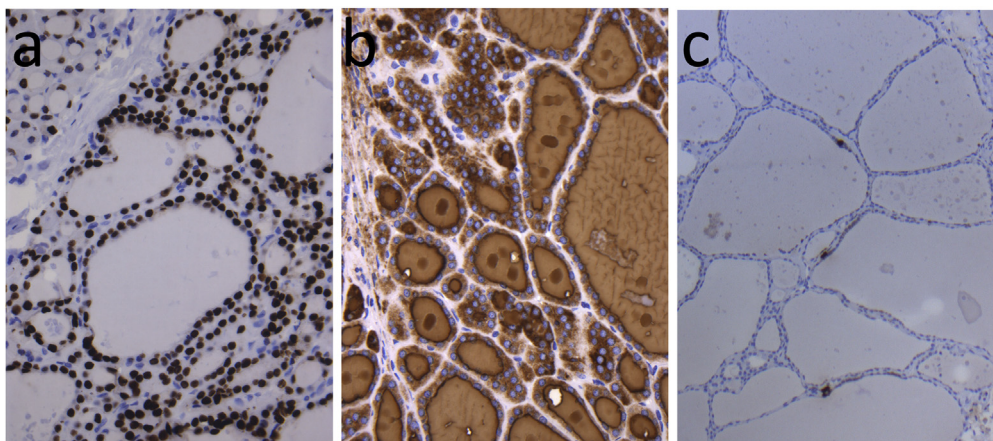


Fig. 6 Immunohistochemistry of thyroid follicular epithelial cells. (a) These cells have strong nuclear positivity for TTF-1 and PAX-8 (not shown). (b) They express thyroglobulin that is strongly stained in the cell cytoplasm and colloid. (c) In contrast to the thyroid follicular cells, the C cells that are members of the family of neuroendocrine cells are scattered in a parafollicular location and are identified by immunolocalisation of the peptide hormone calcitonin.

**Table 1**  Genetic endocrine tumour syndromes

| Syndrome | Prototypical gene(s) | Endocrine manifestations |
| --- | --- | --- |
| MEN1 syndrome | *MEN1* | Pituitary, parathyroid, pancreas, lung, thymus, adrenal cortex |
| MEN4 syndrome | *CDKN1B* | Pituitary, parathyroid, pancreas, lung, thymus, adrenal cortex |
| FIPA syndrome | *AIP* | Pituitary |
| Familial X-linked acrogigantism | *GPR101* | Pituitary |
| HPT-JT syndrome | *CDC73/HRPT2* | Parathyroid |
| MEN2 syndrome | *RET* | Thyroid C cell, phaeochromocytoma |
| VHL disease | *VHL* | Phaeochromocytoma/paraganglioma, pancreas, duodenum and others |
| SDH-driven FPGL 1-5 syndromes | *SDHx*[a] | Phaeochromocytoma/paraganglioma, pituitary, pancreas, ? thyroid |
| Carney triad | *SDHA, SDHB, SDHC* | Paraganglioma |
| Carney−Stratakis syndrome | *SDHB, SDHC, SDHD* | Paraganglioma |
| PTEN hamartoma tumour syndromes | *PTEN, RASAL1* | Thyroid follicular and C cell lesions |
| FAP syndrome | *APC* | Thyroid (papillary carcinoma, cribriform-morular variant), adrenal cortex |
| Li−Fraumeni syndrome | *p53* | Adrenal cortex and others |
| Carney complex | *PRKAR1A, CNC2 locus* | Adrenal cortex, thyroid follicular cell, pituitary, gonads |
| DICER 1 syndrome | *DICER1* | Ovarian sex cord stromal tumours, thyroid follicular cell, pituitary blastoma |
| Lynch syndrome | *MMR*[b] | Adrenal cortex, ? thyroid, pancreas |
| Neurofibromatosis type 1 | *NF1* | Duodenum, pancreas, pituitary, adrenal medulla, adrenal cortex, parathyroid |
| Tuberous sclerosis | *TSC1, TSC2* | Pancreas, rectum, lung, pituitary, parathyroid, pheochromocytoma |
| Mahvash disease[c] | *GCGR* | Pancreas (Alpha cell hyperplasia and neoplasia) |
| McCune−Albright syndrome[d] | *GNAS* | Pituitary, thyroid follicular cell, adrenal cortex, gonads |
| Pacak−Zhuang syndrome[e] | *EPAS1 (HIF2α)* | Paraganglioma, duodenal somatostatin-producing NET |

[a] *SDHx* refers to *SDHA* (FPGL type 5), *SDHB* (FPGL type 4), *SDHC* (FPGL type 3), *SDHD* (FPGL type 1), and *SDHAF2* (FPGL type 2) genes.
[b] MMR (mismatch repair genes) includes: MLH1, MSH2, MSH6, and PMS2.
[c] Aso known as glucagon cell adenomatosis or glucagon cell hyperplasia and neoplasia syndrome.
[d] Non-familial post-zygotic mosaicism.
[e] Somatic.

and better understanding of risk classification of adrenal carcinomas.[42]

Biomarkers have become more complex. It is no longer sufficient to classify a NET based only on the expression of chromogranin-A and Ki-67. The analysis of a Ki-67 labelling index is no longer considered valid when based on eyeball evaluation[46−48] and changes in these parameters are recognised to occur over time.[49] The identification of transcription factors that regulate development of endocrine cells has revolutionised the classification of tumours: PAX-8 and TTF-1 in thyroid,[50] GCM-2[51] and GATA-3[52] in parathyroid, SF-1 for steroidogenic tissues,[53] a family of transcription factors that define pituitary lineages,[39,54] and specific biomarkers that indicate the site of origin of a metastatic NET.[29,55] The importance of keratin and tyrosine hydroxylase to distinguish epithelial from neuroendocrine neoplasms of paraganglia and adrenal medulla cannot be overemphasised when that distinction impacts choices of biochemical surveillance and genetic testing.[56] The availability of antibodies to the many peptide hormones will allow us to increase our understanding of biomarkers in neuroendocrine tissues and tumours and expand the armamentarium of biochemical tests that provide appropriate explanations for clinical symptomatology and early detection of recurrence.

In the 21st century, the complexity of pathology has come to demand deeper understanding of disease than simply pattern recognition.[57] As patients become more aware and involved, they seek expertise and understanding of their health challenges. They no longer rely on a single physician or surgeon, they search the internet for information and expertise, and they want access to their results and consultants. More and more, we are experiencing that patients with endocrine disorders want to know their pathologist, to have confidence that the pathologist understands their disease, and to ensure that their care team members can apply that knowledge to determine interactions that establish their endocrine homeostasis.

## MOLECULAR HISTOPATHOLOGY AND GENETICS OF ENDOCRINE DISORDERS

Advances in molecular biology have allowed diagnosticians to gain insights into morphology-genotype correlations which have improved our understanding of the pathogenesis of endocrine diseases. The application of immunohistochemistry has provided invaluable ancillary biomarkers to facilitate the molecular histopathological classification of endocrine disorders. The most popular examples include but are not limited to antibodies that detect the *BRAF*[V600E] mutation[50,58] and the various *RAS* mutations[59,60] as well as immunohistochemical tests that detect loss of menin (the gene product of *MEN1*), parafibromin (the gene product of *CDC73/HRPT2*),[61] PTEN[50] and APC,[62] immunostains that identify expression due to rearrangements of *RET*[63,64] and *ALK*,[65] nuclear translocation that suggests mutation or activation of beta-catenin,[50,66] immunolocalisation of stabilised p53[50,53,61] and altered localisation of IGF-2.[67]

The understanding of familial predisposition has also allowed clarification of precursor lesions in endocrine tissues[68] and led to a practice shift that requires assessment of tumours for biomarkers of genetic disorders[69] [e.g., menin, p27, parafibromin, SDHB, SDHA, MAX, Fumarate hydratase (FH), 2-Succinocysteine (2-SC), carbonic anhydrase IX, mismatch repair proteins, and alpha-inhibin[70,71]]. Combinations of biomarkers with detailed morphological evaluation of the tumour and the non-tumourous parenchyma has enabled the early detection of an underlying genetic predisposition by facilitating genetic triaging of seemingly sporadic endocrine neoplasms.

## THE FUTURE OF ENDOCRINE PATHOLOGY

Because many of the lesions that are the focus of the discipline of endocrine pathology are increasing in incidence and their pathology is becoming more complex, there is an increased requirement for a deeper understanding of molecular pathology and awareness of a high incidence of familial disease. The field of endocrine pathology is evolving with new challenges, advances in understanding of clinicopathological and genotype-phenotype correlations. The complexity of this field justifies the need for a dedicated subspecialty that bridges pathology with endocrinology and endocrine oncology.

The trend to subspecialisation in pathology has arisen to address the demand for higher quality diagnostics.[57] Pathologists are integral members of the multidisciplinary care team and their presence is required at case conferences and tumour boards. The discussions that ultimately frame management decisions require input from pathologists who understand the prognostic and predictive aspects of this discussion. The development of these programs has taken many forms due to the challenges that result from the expertise of the various radiological and surgical specialists. In some organisations, endocrine pathology is handled in an anatomical model, similar to those other disciplines. At the University Health Network, we have espoused a different model where Endocrine Oncology is a dedicated program in the Princess Margaret Cancer Centre with a core team of endocrine oncologists (in both medical oncology and radiation oncology) and endocrine pathologists who meet on a regular basis with separate teams of surgeons and radiologists. These endocrine oncology tumour boards focus on pituitary and other intracranial lesions with neurosurgeons, head and neck lesions with otolaryngologists and endocrine surgeons, NETs with endocrine and general surgeons as well as the hepatobiliary and transplant surgeons, and adrenal lesions with endocrine surgeons and general surgeons including those who focus on minimally invasive approaches. A recurring theme has been the importance of the core group in managing patients with multiple lesions, for example patients with MEN-1 who have pituitary, parathyroid, thoracic (lung or thymic) and pancreatic NETs. The role of the endocrine pathologist in identifying an ectopic ACTH-secreting appendiceal NET in a patient with previous pituitary Cushing's disease is a prismatic example of the understanding required to correctly diagnose endocrine disorders.

The limiting factor in the development of subspecialty pathology has been the number of pathologists required in any organisation to support every discipline. However, new technologies are allowing a new model of pathology to emerge.[57] Digitisation of traditional glass slides, known as whole slide imaging (WSI), is a transformative technology that can change diagnostic pathology models.[72] Using this new tool, pathology departments can establish new models that have increased numbers of pathologists and a high degree of subspecialisation with sufficient redundancy for each discipline.[57] Advanced pathology informatics provides the foundation for data consolidation to support the provision of the highest quality data.[57] Moreover, this model lays the groundwork for more accurate and objective image analysis, a fundamental tool for the classification of NETs based on proliferation (Volynskaya *et al.*, manuscript in preparation). The ability to harness technology to improve healthcare outcomes will allow successful pathology departments to grow and consolidate resources in a manner that best serves patients to provide the best clinical outcomes.

## CONCLUSIONS

Endocrine pathology is a field with a long and successful past. The growth in importance of endocrine disorders that is being documented in modern medicine heralds a future of critical importance in the healthcare industry. The ability to prepare pathologists to face this challenge will require increased recognition of this area, educational programs that provide the foundation for expertise in endocrine pathology, and wider adoption of a subspecialty model that includes expertise in this field.

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