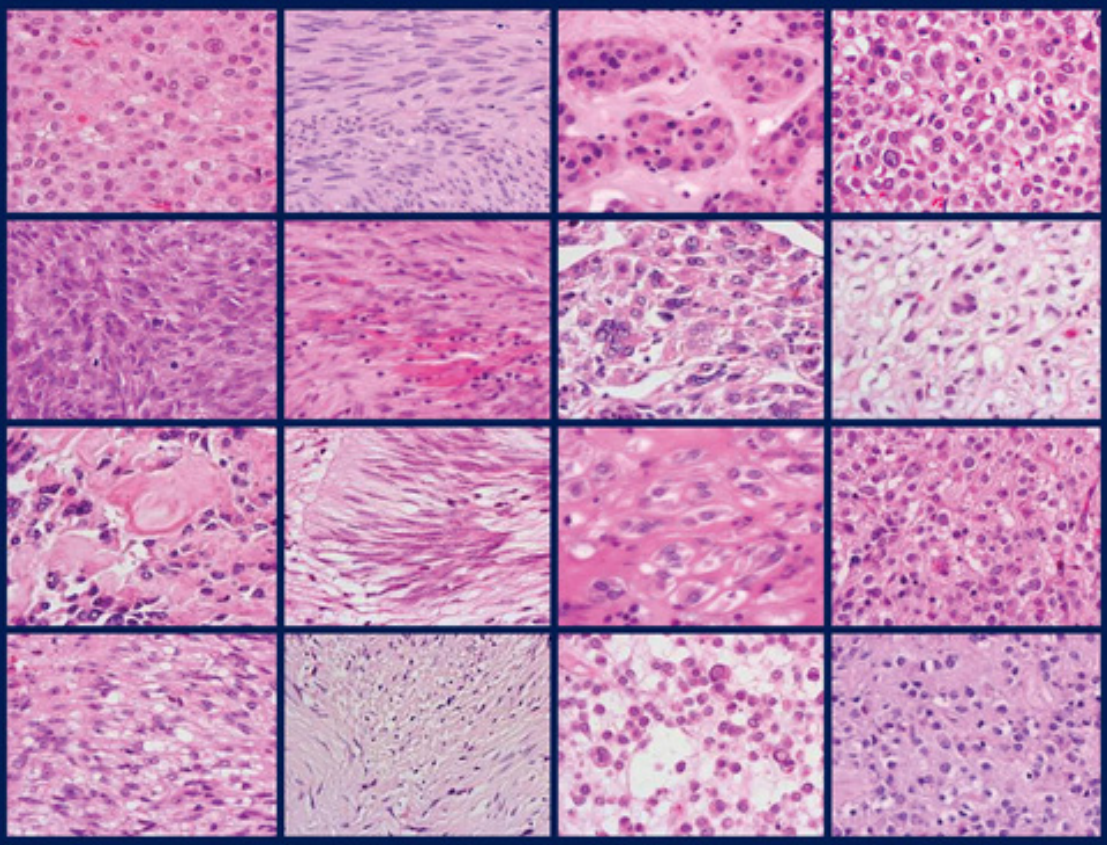
SIXTH EDITION

MORSON AND DAWSON'S GASTROINTESTINAL PATHOLOGY



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with website

WILEY Blackwell

Morson and Dawson's Gastrointestinal Pathology

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Dedication

This book is dedicated to the memory of Dr Basil C Morson, CBE, the original founder, editor and author of this textbook. His legacy of extraordinary contributions to international gastrointestinal pathology will live on.

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Foreword

It is now more than half a century since the late Basil Morson and Ian Dawson produced the first edition of their flagship textbook *Gastrointestinal Pathology*, to be a source of reference to pathologists and clinicians alike on the pathological manifestations of gastrointestinal disease, placed firmly in a clinical context. Subsequent editions, first under the direction of Dr Morson and then by his trainees and mentees in the UK and USA, have perpetuated this ethos, won awards and ensured its legacy. The present contributors are the leading clinical gastrointestinal pathologists worldwide, and such is the standing and reputation of the book that an invitation to contribute is almost invariably accepted. They have succeeded in producing another comprehensive, authoritatively updated and highly readable sixth edition that incorporates contemporary recommendations and guidelines for getting the most out of every pathology specimen and producing the best possible report for managing the patient. The original structure of the book that has stood the test of time remains, apart from one new chapter on lymphoid and other tumours of the large intestine.

Histopathological diagnosis has traditionally been based on the integration of macroscopic and microscopic appearances of a biopsy or resection specimen with the clinical presentation of the patient and remains so to this day. It is quintessentially a visual discipline that requires the written word in any textbook to be complemented by high-quality illustrations to achieve the maximum learning effect. This has been a hallmark of *Morson and Dawson* since inception and remains in this new edition. Indeed, some of the figures have been retained from the original edition because, although now in unfashionable black and white, they are virtually unique examples of pathological specimens that one only rarely sees in twenty-first century practice but illustrate uniquely the advanced stages of untreated disease processes. On the other hand, a panoply of new therapies is leading to modification of classical pathology appearances, the emergence of 'new' lesions and the mimicry of others. These are well illustrated here too.

While microscopic examination of H&E sections remains the mainstay of clinical histopathology, this has been increasingly supplemented over the years, first by immunohistochemistry and more recently by in situ hybridisation. Their applications are amply discussed in every chapter. Major technical advances in quantitative imaging, deep learning and artificial intelligence are beginning to supplement these further, as are the increasingly sophisticated genomic and molecular investigations of DNA, RNA and proteins extracted from disaggregated tissues (and even of circulating cell-free DNA, the so-called liquid biopsy). Used judiciously these will result in evolution, and even revolution, of the diagnostic process, but only if they are integrated with the conventional histopathological morphology as described in this book.

This new edition of *Gastrointestinal Pathology*, still comprehensive in scope, remains a crucial resource for clinical gastrointestinal pathologists, both established specialists and those in training. Its accessibility to gastroenterologists, surgeons, endoscopists, oncologists, radiologists, geneticists and every member of any gastrointestinal multidisciplinary team will ensure that one of Basil Morson's oft-stated aphorisms continues to be fulfilled – 'the view down the microscope should surely be interpreted with awareness that one is looking at part of a patient'.

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Preface and Acknowledgements

We are delighted to see the publication of this, the sixth edition of *Morson and Dawson*. It has been produced some 11 years after the fifth edition, and there have been delays in its production, particularly related to the pandemic. This edition retains the structure and flavour of the fifth edition but there have been additions and changes, described elsewhere. The title retains its position as the UK flagship gastrointestinal pathology text, but we have continued its internationalisation, especially when it comes to the chosen authors.

Sadly, and most importantly, the book's creator and original principal author and editor, Dr Basil C Morson, died, admittedly at the grand old age of 94, during the production of this edition. He was a giant of gastrointestinal pathology, despite working as a single-handed consultant in the small specialist London hospital, St Mark's Hospital. He made an enormous contribution to the medical literature. Indeed, one of us, as his trainee in the early 1980s, recalls that his trainees used to consider him the most famous pathologist in the world! Well after his retirement, he maintained a strong interest in the title, even into his tenth decade, and was always delighted to hear about developments and the progress of the book.

There have also been changes in the editors. We have lost two editorial stalwarts, Professor Bryan Warren, who died at the young age of 53, a victim of a disease of which he was a world expert, and Professor Geraint Williams, who has retired. We were delighted when Geraint accepted the offer to write the foreword to this edition. He had been a very important member of the editorial team through several editions and had been the lead editor for the fourth edition. There are three new editors, Professors Maurice Loughrey and Kieran Sheahan, both from the island of Ireland, and Professor Adrian Bateman, from Southampton, UK, who has agreed to take on the role of lead editor for this sixth edition. They bring with them vitality and relative youth to the editorial team.

Gastrointestinal pathology continues to develop into a very large and diverse subject. So, the book is very much multi-author and also international in its authorship. Leaving behind most of the traditional but aesthetically pleasing black-and-white photographs of earlier editions, the illustrations are, we believe, of high quality and mainly 100% colour. We have ensured that all authors reflect the very considerable advances in molecular pathology, immunohistochemistry and pathological practice that have occurred in the last decade.

Finally, we would like to sincerely thank all of our friends and colleagues who have provided illustrations for this book. They are too numerous to mention individually here, but relevant acknowledgements have been made in the legends to those illustrations. We are also extremely grateful to our colleagues and friends at Wiley, especially Moyuri Handique and Jenny Seward, for their help, professionalism and goodwill in the production of this edition.

Adrian C Bateman
Neil A Shepherd

About the companion website

This book is accompanied by a companion website.

www.wiley.com/go/morsondawson6e 

This website includes:

- Images from the book as downloadable PowerPoint slides

PART 1

Oesophagus

CHAPTER 1

The normal oesophagus: anatomy, specimen dissection and histology relevant to pathological practice

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Anatomy

The adult oesophagus is a muscular tube about 250 mm long, extending from the pharynx, at the cricoid cartilage opposite the sixth cervical vertebra, to the oesophago-gastric junction, about 25 mm to the left of the midline, opposite the tenth and eleventh thoracic vertebrae. It has longitudinal mucosal folds and, when empty, a narrow lumen. For endoscopists, the distance from the incisor teeth to the upper end of the oesophagus is about 150 mm and to the oesophago-gastric junction about 400 mm, depending, clearly, on the height of the subject. The oesophagus pierces the left crus of the diaphragm and has an intra-abdominal portion about 15 mm in length. Its principal relations, important to the pathologist in assessing the local spread of cancer, are with the trachea, the left main bronchus, the aortic arch, the descending aorta and the left atrium.

The arterial supply of the oesophagus is by the inferior thyroid, bronchial, left phrenic and left gastric arteries and by small branches directly from the aorta. Its veins form a well-developed submucosal plexus draining into the thyroid, azygos, hemiazygos and left gastric veins. It provides important connections between the systemic and portal venous systems. Lymphatic channels from the pharynx and upper third of the oesophagus drain to the deep cervical lymph nodes, either directly or through the paratracheal nodes and also to the infrahyoid lymph nodes. From the lower two-thirds, they drain to the posterior mediastinal (para-oesophageal) lymph nodes and then to the thoracic duct. From the infra-diaphragmatic portion of the oesophagus, drainage is to the left gastric lymph nodes and a ring of lymph nodes around the cardia. Some lymph vessels may drain directly into the thoracic duct. In its upper part, the oesophagus is innervated by the glossopharyngeal nerve, and throughout its length, it is supplied by fibres of the vagus nerve and local sympathetic ganglia.

The lower end of the oesophagus is anchored posteriorly to the pre-aortic fascia and is surrounded by the phreno-oesophageal ligament, which blends into the muscularis propria of the oesophagus. This arrangement allows some degree of movement and rebound. Dissection studies indicate that no discrete anatomical sphincter is present, but there are differences of opinion as to whether, and if so how, the muscle at the oesophago-gastric junction is modified. One anatomical study [1] has excluded the presence of any thickening of the muscularis mucosae or of the circular muscle coat but has described the separation of obliquely arranged inner circular muscle fibres into fascicles, which continue into the stomach to form the circular muscle layer. However, another investigation [2] describes definite thickening of the inner circular muscle coat. Both studies have concluded that the arrangements they describe might, and probably do, act as a functional sphincter.

The oesophageal wall in cross-section (Figure 1.1) can be divided macroscopically into the following:

- Stratified squamous epithelium
- Lamina propria
- Muscularis mucosae
- Submucosa
- Muscularis propria
- Adventitia

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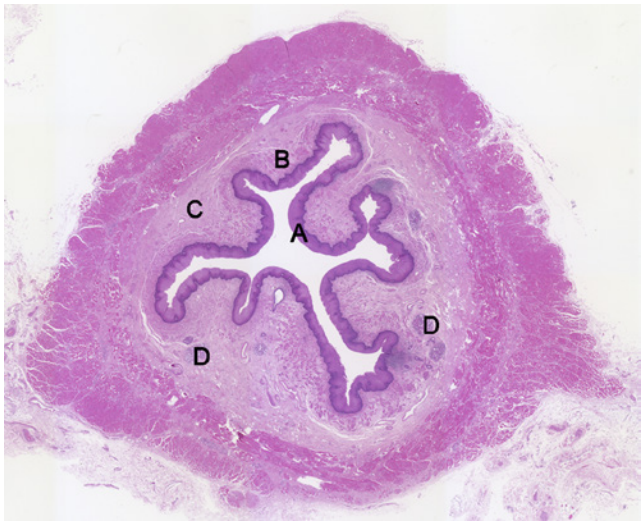

Figure 1.1 The wall of the oesophagus. In this cross-section, A is the squamous epithelium-lined mucosa and B is the muscularis mucosae, separated from the mucous membrane by the lamina propria. C is the submucosa which contains the oesophageal submucosal glands (D), and the circular and longitudinal layers of the muscularis propria are outside the submucosa.

Practice points 1.1

- The oesophagus shares a similar structure, essentially four major layers, with all other parts of the luminal gastrointestinal tract
- The assessment of the depth of spread by tumours through these various layers of the wall is of critical importance for staging and prognostication
- Although the submucosal glands of the oesophagus secrete various substances, importantly mucin, the major function of the oesophagus is to transmit food and fluids to the stomach from the upper digestive tract

Histology

The mucosa

The squamous-lined mucosa is about 500 to 800 microns thick and is composed of non-keratinising stratified squamous epithelium with a subjacent lamina propria resting on the underlying muscularis mucosae. The squamous epithelium (Figure 1.2) has a basal zone consisting of several layers of cuboidal or rectangular basophilic cells with dark nuclei, in which glycogen is absent. It occupies about 10 to 15% of the thickness of the normal epithelium, although it may be thicker in the last 20 mm of the squamous-lined oesophagus. Occasional mitoses are evident in the basal and parabasal cell layers. Above the basal zone, the epithelial cells are larger and become progressively flattened, but even on the surface, they retain their nuclei. Keratohyaline granules are not usually present in the surface cells of the normal epithelium. However, glycogen is abundant.

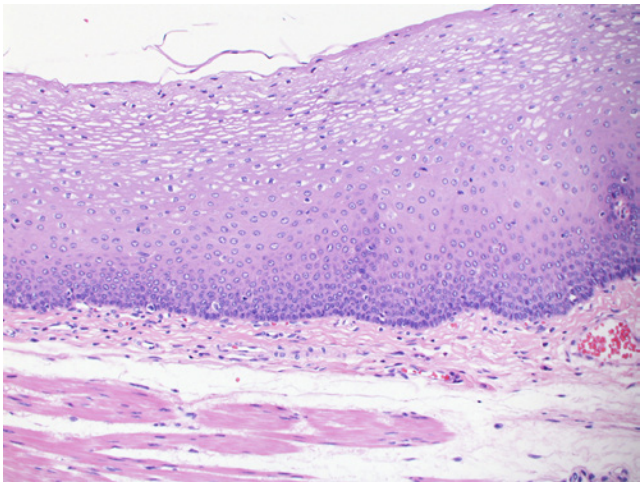

Figure 1.2 The normal stratified squamous epithelium of the oesophagus. It has no keratinisation or well-developed glandular layer. Note the thickness of the basal cell layer and the height of the papillae.

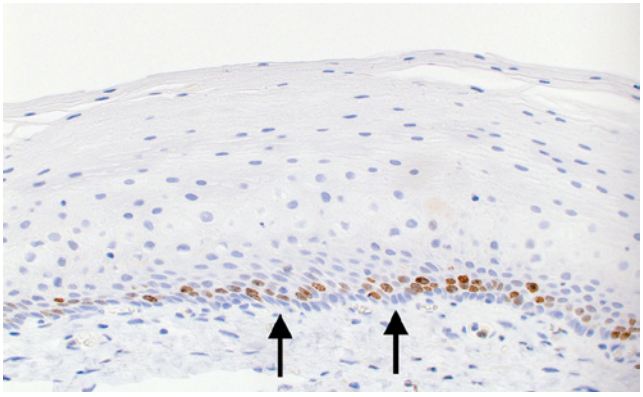

Figure 1.3 Ki-67 immunostaining of the normal oesophageal mucosa. The basal cells (arrows) on the basement membrane do not stain, but parabasal cells are positive for Ki-67.

Ki-67 immunostaining usually shows a negative reaction in the basal layer on the basement membrane and a positive reaction in the parabasal layers. Epithelial stem cells may be present in the basal layer. The presence of Ki-67-positive cells in more than three cell layers is an abnormal feature, consistent with the effects of gastro-oesophageal reflux disease (Figure 1.3).

Single intra-epithelial lymphocytes ('squiggle' cells) lying between the squamous cells are common, particularly in the lower half of the mucosa, and in this situation, their convoluted nuclei may be confused with the nuclei of neutrophils. They are a normal feature. Characterisation using monoclonal antibodies has shown them to be T-lymphocytes [3]. Langerhans cells are antigen-presenting cells that are demonstrable, by electron microscopy and metal impregnation techniques, as sparsely distributed

ovoid forms with radiating dendritic processes occurring in all layers of the oesophageal epithelium [4]. They are positively stained with antibodies against S-100 protein and also react with monoclonal antibodies against HLA-DR and CD1. They contain calcitonin gene-related peptide (CGRP), which may serve as an immunomodulator. The number of Langerhans cells and the intensity of their immunoreactivity for CGRP are increased in reflux oesophagitis [5]. They contain Langerhans granules (Birbeck granules), seen on electron microscopic examination.

Both melanocytes and non-melanocyte argyrophil cells are randomly distributed in the basal layer of the epithelium, the former usually as small groups and the latter singly [6,7]. These cell types are presumably the origin of primary malignant melanomas and small-cell undifferentiated (oat-cell) carcinomas, respectively, that occur at this site. Merkel cells are also present in the epithelium.

Transmission electron microscopy (TEM) studies of the squamous epithelium have broadened our understanding of the micro-anatomy [8–13]. Basal cells are cuboidal or columnar, with large, centrally placed nuclei and relatively simple cytoplasm containing few organelles. They are attached to the basement membrane by frequent hemidesmosomes. Prickle cells show numerous keratin filaments, relatively abundant glycogen, a prominent Golgi apparatus and more numerous desmosomes. The squamous cells of the superficial or functional zone become increasingly flattened towards the lumen. They contain phospholipid material and have a coating of acid mucosubstance, which is likely to have a protective function. Scanning electron microscopy shows a complex pattern of micro-ridges lining the lumen. Membrane-coated granules, 0.1–0.3 μm in diameter, are present in the intermediate and superficial zones of the oesophageal epithelium. As well as being the source of mucosubstances, they contain acid hydrolases, which, when secreted into the intercellular space, may be responsible for the reduction of desmosomes exhibited by squamous cells as they approach the luminal surface.

Free-ending nerves are located in the intercellular spaces of the squamous epithelium and reach the subepithelial nerve plexus. These nerves probably mediate oesophageal pain. Cell proliferation studies have demonstrated a slower cell cycle time in basal cells overlying papillae in comparison with the inter-papillary basal cells [14]. The turnover time of the oesophageal epithelium is about four to seven days in rats and mice. The corresponding period in humans is said to be 10 days or less, although definitive data are not available.

The lamina propria consists of loose connective tissue containing small numbers of lymphocytes, mostly helper T-cells, plasma cells and occasional eosinophils and mast cells. Small collections of lymphocytes and plasma cells may be aggregated around the ducts of the oesophageal submucosal glands. The oesophageal blood vessel anatomy is increasingly important for endoscopic reasons and will be described in detail below.

The muscularis mucosae varies in its structure in different parts of the oesophagus. In the upper oesophagus, it consists of isolated or irregularly arranged muscle bundles rather than forming a continuous sheet, but in the middle and lower thirds, it forms a continuum of longitudinal and transverse fibres and reaches 300 μm in thickness at the squamo-columnar junction. In the resected oesophagus, thick collections of fine irregular muscle fibres are evident at sites of vious biopsy.

Submucosa

The submucosa contains the oesophageal submucosal glands (deep glands, oesophageal glands proper), Meissner's plexus and a ramifying lymphatic plexus within a loose connective tissue network, which accounts for the early and extensive submucosal spread of oesophageal carcinoma. The oesophageal submucosal glands are arranged in rows parallel to the long axis, and although scattered, they are relatively more concentrated at the upper and lower ends of the oesophagus [15]. They are compound tubuloalveolar in type and resemble labial salivary glands, containing both mucous and serous secretory cells and oncocytes, with surrounding myo-epithelial cells, anchoring them to the underlying basement membrane. The mucous cells contain sulphomucins. Many glands do not contain serous cells. From two to five lobules drain into a common duct lined by a flattened cuboidal epithelium initially, which becomes stratified squamous in type and surrounded by lymphocytes and plasma cells after passing obliquely through the muscularis mucosae (Figure 1.4). The presence of oesophageal submucosal glands and/or their ducts is

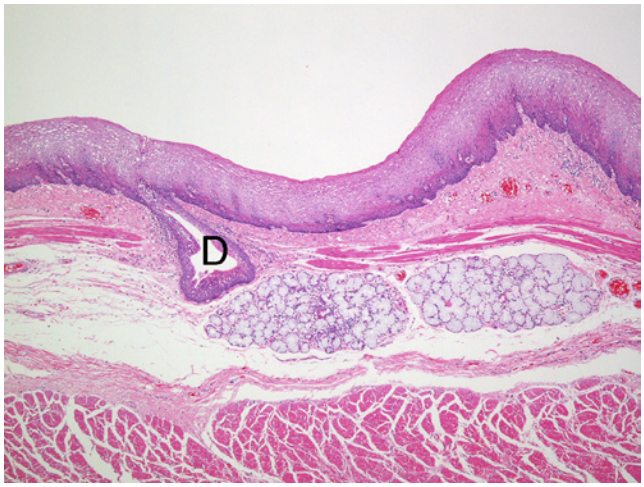

Figure 1.4 The submucosal gland of the oesophagus. The terminal portions consist of mucous cells. An oesophageal gland duct (D) is evident.

presumptive evidence that any sampled biopsy material derives from the true anatomical oesophagus, of special importance in the diagnosis of Barrett's oesophagus.

Muscularis propria

The muscularis propria consists of well-developed circular and longitudinal coats. In its upper part, these are striated, and both oxidative (fast-twitch) and glycolytic (slow-twitch) fibres are present [16]. There is a gradual change to smooth muscle in the upper and middle thirds, whereas in the lower third, both coats are entirely composed of smooth muscle without clear evidence of sphincter formation. A well-defined myenteric nerve (Auerbach's) plexus is present at all levels, but there appears to be no well-formed submucosal plexus. Three neuronal types are identifiable [17,18]. One is argyrophilic, multi-axonal and, likely, sympathetic and sends out numerous dendrites and axons to surround other neurons in the same and adjacent ganglia but does not directly supply muscle. The second type is not argyrophilic but cholinergic and probably parasympathetic, supplying the muscle. The former likely has a coordinating function and the latter a motor function. A third type of fibre, probably part of the communicating system, is rich in vasoactive inhibitory peptide (VIP). Such fibres are commonly associated with sphincteric mechanisms [18]. There are also numerous intrinsic fibres containing neuropeptide Y [19]. Ganglion cells decrease in number with age [20], but the smooth muscle does not undergo corresponding atrophy.

Adventitia

The adventitia of the oesophagus is a thick layer of coarse connective tissue around the oesophagus and is seen to surround the oesophagus in resection specimens. It contains blood vessels; lymphatics and lymph nodes; multiple branches, anterior and posterior, of the vagus nerve; and other neural structures. Its comprehensive examination is of particular importance in such resection specimens, as here, proximity of tumour to the circumferential surgical resection margin and the pleural surfaces will be evident and assessable (vide infra). The adventitia is in continuity with the adjacent mediastinal connective tissues.

Vascular structures in the mucosa and submucosa of the oesophagus

The palisade veins, also known as longitudinal vessels, are located within the mucosa of the upper and lower oesophagus [21,22]. They can be observed endoscopically in the areas of the upper and lower oesophageal sphincters [21–23]. The lower palisade veins are always located within a 30 mm length of the lower oesophageal sphincter and are not found in the middle oesophagus or stomach [22–24] (Figure 1.5). Larger veins in the submucosa of the stomach and proximal oesophagus run through the muscularis mucosae into the lamina propria mucosae and exhibit a longitudinal pattern along the oesophageal long axis in the lower oesophageal sphincter. Endoscopically, mucosal veins show a distinct palisade arrangement in the lower oesophagus and a mesh-like network pattern in the middle oesophagus (Figure 1.6). Palisade veins can be observed in

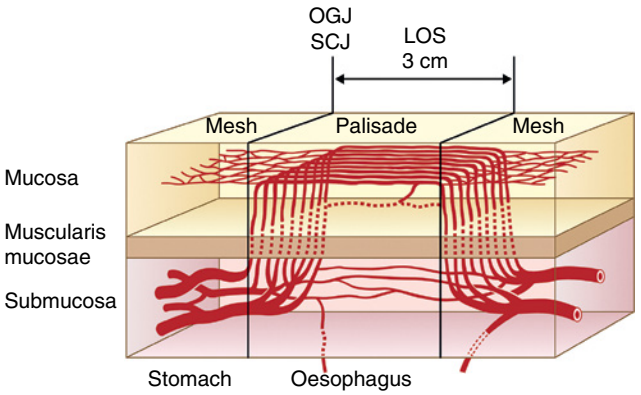

Figure 1.5 A schema of the palisade veins in the lower oesophageal sphincter. They are always located within 3 cm of the lower oesophageal sphincter (LOS). The squamo-columnar junction (SCJ) usually coincides with the oesophago-gastric junction (OGJ). Mesh: mesh-like network pattern; palisade: palisade pattern. Adapted from [22].

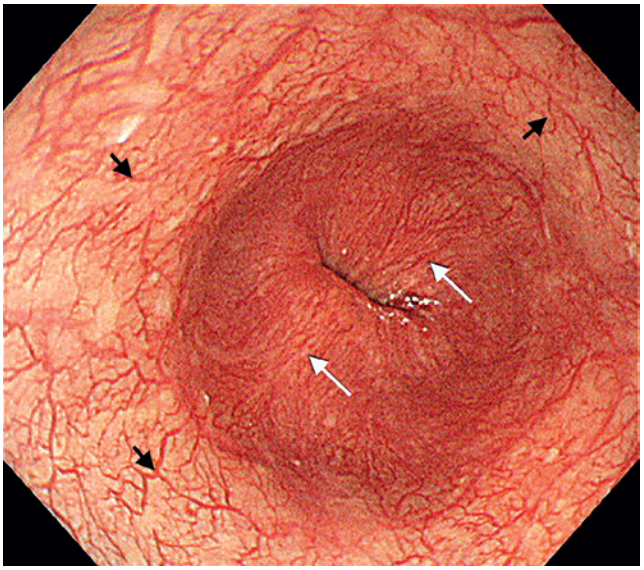

Figure 1.6 An endoscopic image of the middle and lower oesophagus. A mesh-like pattern of vessels (black arrows) is evident in the marginal area, whereas a palisade pattern (white arrows) can be seen in the central area (lower oesophagus) of the image. Courtesy of Dr K. Kumagai.

Barrett's oesophagus, as well as squamous-lined mucosa in the oesophagus. Therefore, although in Western countries the endoscopic definition of the oesophago-gastric junction has usually been the upper limit of the gastric mucosal folds [25], in Japan it is usually defined as the lower limit of the palisade veins [26].

Histologically, in transverse sections of the lower oesophagus, large veins exceeding 100 μm in the minor axis are observed much more frequently in the lamina propria of the lower oesophageal sphincter than in the middle oesophagus, and these are considered to be the palisade veins seen at endoscopy [27]. The practical use of palisade veins for defining the origin of tissue samples in surgical pathology is well described [27]. Veins greater than 100 μm in diameter are not histologically evident in gastric mucosa with or without intestinal metaplasia. Long and straight veins in sections cut longitudinally along the oesophagus are observed histologically within the mucosa in columnar-lined oesophagus as well as squamous epithelium-lined oesophagus (Figures 1.7 and 1.8) in surgical and endoscopic resection specimens. Therefore, the histologically defined lower ends of palisade veins are definitely considered to represent the oesophago-gastric junction [27] in a way similar to the endoscopic demonstration. So, when palisade veins are seen through metaplastic columnar epithelium, a diagnosis of Barrett's oesophagus can be made by endoscopy alone [26]. However, in slides of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) samples, many dilated veins are frequently observed as a result of treatment. Differentiating these veins from palisade veins can be difficult and requires careful comparison.

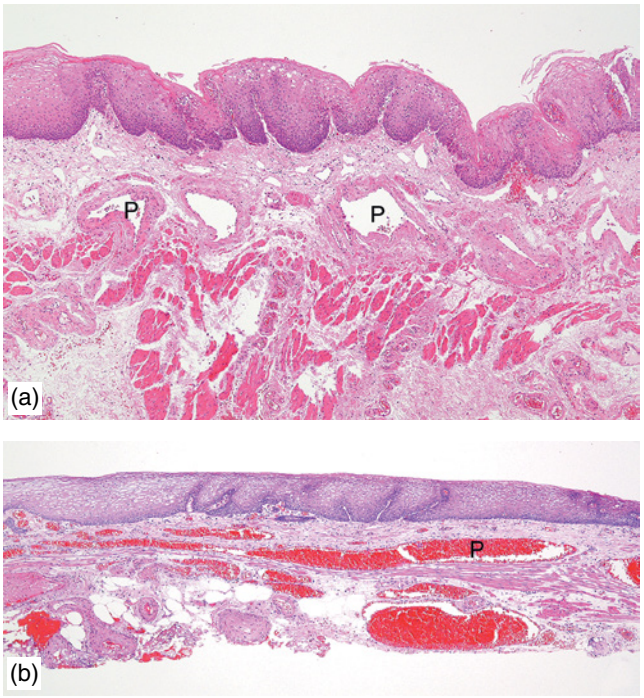

Figure 1.7 Histology of the lower oesophagus lined by squamous epithelium. (a) Transverse section. Large palisade veins (labelled P) are observed in the mucosa. (b) Longitudinal section. A longitudinally sectioned large palisade vein (labelled P), 3 mm in length, is evident in the mucosa. Courtesy of Drs T. Arai and J. Aida.

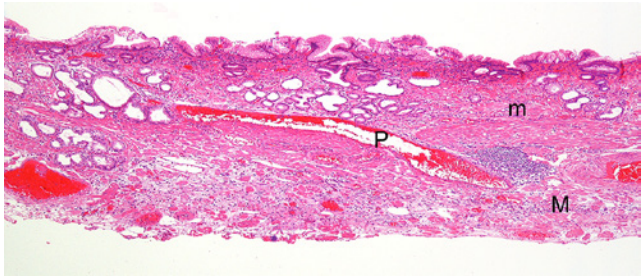

Figure 1.8 Histology of the lower oesophagus lined with columnar epithelium. A longitudinally sectioned large palisade vein (labelled P), 1.6 mm in length, is evident between the double muscularis mucosae in the mucosa. M: original muscularis mucosae; m: newly developed muscularis mucosae. Courtesy of Dr J. Aida.

Tissues adjacent to the oesophagus, including the pleura

These are of some importance as they are or may be present in resected oesophageal specimens. The proximal stomach is almost universally present in such specimens, whereas the pharynx and spleen are occasionally seen in specimens resected with the oesophagus. The trachea, bronchus, lung, diaphragm, azygos vein, thoracic duct, thymus and aorta can also be present in oesophageal resection specimens. Although usually termed the *circumferential* resection margin of the oesophagus, it is important to note that, especially on the right but also on the left, a sizable proportion of the circumference of oesophageal resection specimens is actually invested not by adventitial connective tissues, thus constituting a true surgical margin, but by pleura, which all radical oesophago-gastrectomy specimens will possess. Involvement of the circumferential margin can be influenced by surgical quality, but a surgeon can do little about pleural involvement. We advocate accurate identification of the pleura on both sides and painting, preferably by coloured gelatine, only of the true circumferential surgical margin to allow differentiation of these structures in histological sections.

Location of the oesophago-gastric junction

Precise definitions of the oesophago-gastric junction are essential before an accurate diagnosis of columnar-lined oesophagus (CLO) (see Chapter 5) can be made.

Anatomically, the definition of the oesophago-gastric junction is the line between the angles of the opened oesophagus and gastric curvature. This definition can be used for surgically resected materials. Clinically, however, the location of the oesophago-gastric junction is controversial [28]. The distance between the anatomical oesophago-gastric junction and the squamo-columnar junction on macroscopic examination of autopsy specimens has ranged from 0–10 mm with a mean of 3 mm [29] to 5–21 mm with a mean of 11 mm [30].

In North America and European countries, the endoscopic definition of the oesophago-gastric junction is the upper limit of the gastric folds. However, this upper limit shows considerable vertical movement during endoscopy [26]. When a small volume of air is present in the oesophagus or at expiration, the upper end of the mucosal folds moves rostrally. When a large volume of air is present or in deep inspiration, the upper end of the columnar mucosal folds moves caudally. Therefore, the upper limits of the columnar mucosal folds are not in a constant position. Palisade vessels are always evident within the oesophagus [22], are observed within the lower oesophageal sphincter and can be used to define the oesophago-gastric junction. So, in Japan, the oesophago-gastric junction is defined endoscopically as the lower limit of the palisade vessels [29]. Based on this definition, many cases may actually be defined as representing ultrashort segment columnar-lined oesophagus. Pathologists should always pay attention to the true origin of any biopsy specimen from the mucosa around the oesophago-gastric junction.

Oesophageal cardiac glands (superficial glands, mucosal glands) are small mucous glands in the lamina propria. They are branched simple tubulo-alveolar glands located mainly in the lower and upper oesophagus. Oesophageal cardiac glands beneath the oesophageal squamous epithelium at the squamo-columnar junction show continuity with the gastric cardiac mucosa and can be observed at endoscopy through the squamous epithelium in about half of all subjects examined. However, cardiac glands are histologically evident at or around the oesophago-gastric junction in almost all individuals (Figure 1.9). The maximum overlap of the squamous epithelium and cardiac glands extending continuously from the gastric cardia, as demonstrated by histological and endoscopic examination, may be up to 15 mm. Endoscopically, oesophageal cardiac glands beneath the squamous epithelium in the oesophago-gastric junction zone usually appear yellowish in colour and are flat or slightly elevated. Columnar-lined islands are also observed endoscopically in squamous mucosa and are similar in colour to those of the gastric cardiac mucosa, being unstained with Lugol's iodine. Columnar islands can often be found in the distal 10 mm of the oesophagus. They are observed in about half of all patients with oesophageal or gastric carcinoma.

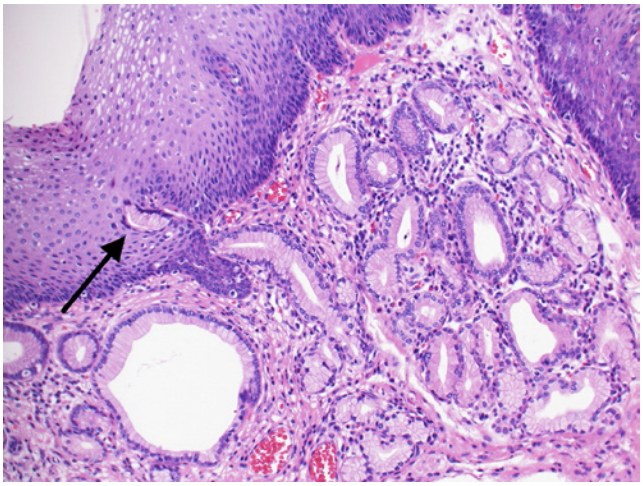

Figure 1.9 The oesophageal cardiac glands (also known as superficial or mucosal glands) beneath squamous epithelium in the oesophago-gastric junction zone. Mucous gland lobules are present. Part of a cardiac-type gland (arrow) is apparent in the squamous epithelium.

In cardiac mucosa adjacent to the squamo-columnar junction, most of the gland cells are mucous in type and stain strongly with periodic acid–Schiff (PAS). Occasional cells near the upper ends of the glands, close to the squamous junction, may secrete both sialomucins and sulphomucins [31]. Parietal cells, morphologically identical to those in the fundic glands, are present in small numbers (oxyntocardiac glands), and occasionally, chief cells are present as well. Numerous endocrine cells, some of which are argentaffin and others argyrophil, are found in this region [32]. Lymphoid follicles are also common in the deeper part of the mucosa or extend through the muscularis mucosae into the submucosa.

Pancreatic tissue (Figure 1.10) may be seen in the mucosa at the oesophago-gastric junction: it is recognisable by the presence of variably sized nests or lobules of acinar tissue 0.2–1.6 mm in diameter, admixed with cardiac glands, and composed of cells with basally located, small, round and uniform nuclei and abundant cytoplasm. These structures appear eosinophilic and granular in the apical and middle portions and basophilic in the basal area. Some mucous cells may be intermingled [33]. Because of their resemblance to pancreatic exocrine cells and their immunopositivity for lipase, the term *pancreatic acinar metaplasia* has been used to describe this feature. Some have suggested an association with gastritis, but subsequently it has been recognised as a common feature in patients attending for elective upper gastro-intestinal endoscopy and is not specifically associated with any clinical or histological abnormalities of the oesophagus or stomach [34]. Similar foci have been described in the gastric antral and body

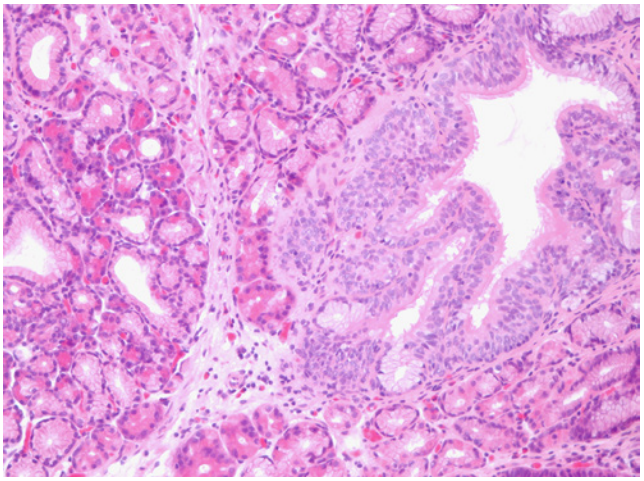

Figure 1.10 Pancreatic metaplasia and ciliated epithelium in the mucosa at the oesophago-gastric junction. Pancreatic acinar cells with eosinophilic cytoplasmic granules are present amongst cardiac-type glands. The ciliated epithelium is histologically similar to that of bronchial pseudo-stratified columnar epithelium.

mucosa but appear to be much less common at these sites, although they have been reported in some 3% of antral biopsies from children [35].

Multilayered epithelium (ME) or squamous metaplasia-like change may be evident in the oesophageal cardiac glands beneath the squamous epithelium and in cardiac mucosa adjacent to it. There may also be a pseudo-stratified (partly ciliated) columnar epithelium, often merging with the squamous metaplasia-like change [36]. When histological examination of a biopsy specimen reveals pancreatic acinar metaplasia, multilayered epithelium, squamous metaplasia-like change or pseudo-stratified columnar epithelium with occasional cilia, we firmly believe that that tissue can yet derive from the 'normal' mucosa of the oesophago-gastric junction zone and does not necessarily infer Barrett's oesophagus (see Chapter 5).

Practice points 1.2

- The submucosal glands and their ducts, passing into the mucosa of the oesophagus, provide in biopsy material (especially of Barrett's oesophagus) definitive evidence of an origin in the native oesophagus.
- Despite its importance in preventing reflux of gastric contents, there is no good evidence for a formed sphincter at the oesophago-gastric junction.
- Little recognised in Western endoscopic and pathological practice, the palisade blood vessels of the lower oesophagus are important landmarks and provide good evidence for the anatomic level at endoscopy and in histological sections.

Handling of endoscopic and resection oesophageal specimens

Endoscopic resection specimens

EMR and ESD are increasingly important for diagnosing and treating neoplasia in the oesophagus. They can be used for the removal of small benign tumourous nodules, such as granular cell tumours and other small connective tissue tumours in the submucosa, but EMRs are also employed as a 'big biopsy': for instance, for the definitive diagnosis of well-differentiated squamous cell carcinoma when multiple previous biopsies have been unable to fully confirm the diagnosis. Of increasing importance is their use in the management of early neoplasia complicating Barrett's oesophagus.

Although somewhat dependent on the endoscopic methodology used, before fixation, they can be stretched to reflect the size and shape as that in the body and then pinned to a board with the mucosal aspect uppermost. The specimen(s) should then be immersed in a large container of formalin and fixed for at least half a day or overnight. Either initially or after fixation, they can be painted to demonstrate peripheral and deep margins of excision. India ink, coloured paints and coloured gelatine can be used, depending on local laboratory preferences. For specimens that have been resected piecemeal, pinning and fixation should be performed by an endoscopist aware of the actual configuration of the lesion in vivo to enable more precise restructuring and assessment of ultimate (especially peripheral) resection margins.

It is recommended that fixed specimens obtained by EMR and ESD are cut into slices 2–3 mm thick for serial sectioning and microscopic examination. The lines of sectioning should be at right angles to the line, forming a tangent to the resection margin close to the tumour [37].

Surgical resection specimens

Oesophagectomy and oesophago-gastrectomy operations are most commonly undertaken for carcinoma of the oesophagus. In the Far East, this is usually for squamous cell carcinoma, whereas in Western countries, adenocarcinoma complicating Barrett's oesophagus is now overwhelming the commonest indication for these operations. Increasingly, neo-adjuvant chemo(radio)therapy has been used, and this may make identification of the site of the tumour difficult and may require extensive blocking of the oesophagus to ensure that the entire tumour site has been assessed histologically. This chapter will give guides as to the appropriate macroscopic preparation and assessment of these specimens, but the interested reader is referred to guidelines and protocols published by Japanese, UK and US authorities for a comprehensive guide to the assessment of such specimens [38–40].

Surgically resected specimens should be opened longitudinally in a standard way. We recommend standard opening ventrally. The part of the oesophagus containing the tumour may then be left unopened with an appropriate fixative-soaked wick to ensure internal fixation. Alternatively, that part can be opened in a standard way (ventrally) with the circumferential margin previously painted to aid accurate assessment of margins of excision. At this time, whether the tumour is opened or not, it is important for the prosector to identify the pleural surfaces and ensure that these can be accurately differentiated, at the time of histological assessment, from the true circumferential resection margin by appropriate painting (vide supra). Further, these specimens undergo dramatic shortening immediately after surgery because of contraction of the muscularis propria such that the oesophageal segment is often only half the length it was in situ. Therefore, efforts should be made to ensure that these specimens are received in the laboratory as soon as possible so that they can be stretched and pinned on a corkboard to reflect the size before resection.

Although some authorities recommend that oesophagectomy specimens should *always* be fixed unopened through the tumour, we believe that there are times, especially in early cancer, in multifocal dysplasia and superficial cancer (especially that complicating Barrett's oesophagus) and when neo-adjuvant therapy has effectively ablated the tumour, that opening the specimen is appropriate to allow accurate identification of those parts of the specimen for submission for histological assessment. After neo-adjuvant therapy, only an area of superficial scarring of the mucosa may be seen on opening, and this may be less easy to appreciate in transverse sections of a specimen previously left unopened. Assessment of these specimens should not be beholden to blanket national and international 'rules' but should be determined by the requirements of the individual case and by local laboratory practices.

In a specimen left unopened, a large sharp knife should be used to section the entire tumour area transversely with identification of the orientation achieved by differential painting or another method favoured by the laboratory. These slices can then be submitted for histology in their entirety, usually in big blocks, such that all adventitial tissues, para-oesophageal lymph nodes and pleural surfaces can be assessed along with the true circumferential resection margin, previously identified by painting. We recommend coloured gelatine for this purpose as it adheres very effectively to the surface, is readily identified in histological sections and does not run or spread like other fluids used in laboratories for this purpose.

It is important to ensure that proximal and distal surgical resection margins are assessed histologically, and separate doughnuts from these margins should always be submitted for histology in their entirety, as oesophageal cancer—both squamous cell carcinoma and adenocarcinoma—can demonstrate discontinuous spread, often because of submucosal lymphovascular spread, with involvement of margins at some distance from the primary tumour. The proximal and distal resection margins can be assessed in sections taken parallel to the margins and/or in longitudinal sections perpendicular to the margins [38,39].

Superficial carcinoma can usually be distinguished from advanced carcinoma by macroscopic observation of cut surfaces of the tumour or by determining whether a superficial tumour is fixed to the muscularis propria. If not fixed, the tumour will slide over the muscularis propria when only slight force is applied to the mucosa, indicating that it is likely a superficial carcinoma without invasion to the muscularis propria. We recommend that, in cases of superficial carcinoma, the specimen is sliced parallel to the long axis of the oesophagus. Whole step-sections can then be prepared [38,40].

In more advanced carcinoma, be that squamous cell carcinoma or adenocarcinoma, it is clearly important to extensively sample the most deeply invasive tumour. One or more representative slices of the tumour at the site of deepest invasion, estimated by inspection and palpation, parallel and perpendicular to the oesophagus, should be blocked and submitted for histopathological examination to demonstrate the deepest aspect of the tumour and its relationship to the layers of the oesophageal wall, the adventitial tissues and, critically, the circumferential resection margin and pleural surfaces [38–40].

Practice points 1.3

- EMR and ESD specimens are increasingly important for the accurate diagnosis of neoplastic oesophageal diseases and for providing staging data to drive further patient management.
- Attention to appropriate fixing, dissection, sampling and accurate histological analysis are all critical for optimal assessment of such specimens.
- No one should mandate whether an oesophageal resection specimen is opened or left closed to fix. Each specimen should be assessed individually. There are circumstances where it is undoubtedly appropriate to fully open such a specimen, preferably ventrally.

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