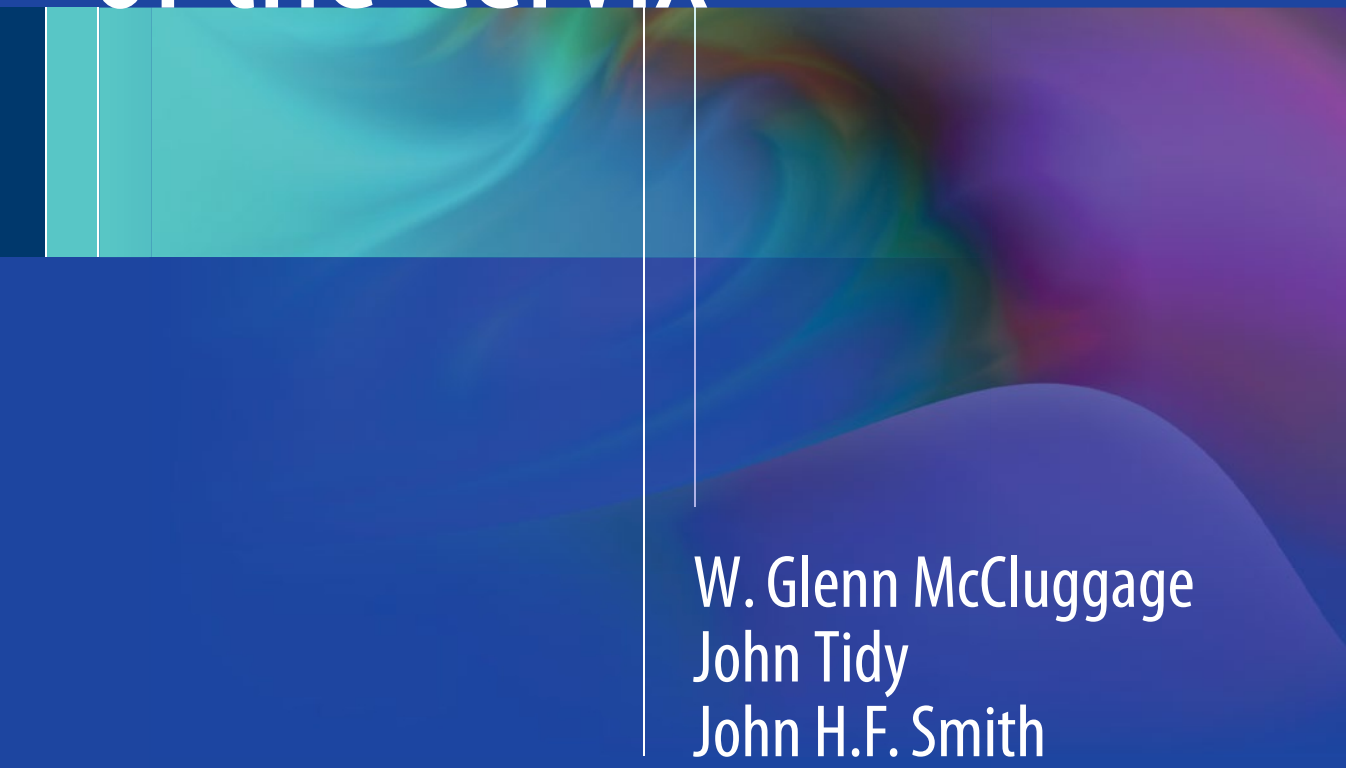
Cellular Pathology of Glandular Lesions and Uncommon Neoplasms of the Cervix



W. Glenn McCluggage
John Tidy
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W. Glenn McCluggage
Department of Pathology
Royal Victoria Hospital
Belfast
UK

John H.F. Smith
Department of Histopathology
and Cytology
Royal Hallamshire Hospital
Sheffield
UK

John Tidy
G18
Royal Hallamshire Hospital
Sheffield
UK

ISBN 978-1-4471-2209-8 ISBN 978-1-4471-2210-4 (eBook)
DOI 10.1007/978-1-4471-2210-4
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014950793

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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Introduction

Cervical histopathology specimens, mainly punch biopsies and loop excisions but also hysterectomy specimens, form a significant proportion of the workload of many surgical pathology laboratories. Most biopsies are performed because of an abnormality detected in a cervical cytology specimen taken during the course of an organised population cervical screening programme. The majority of biopsies are performed because of a suspected squamous abnormality. Although there can be problems in interpretation, the differential diagnosis of squamous lesions is relatively limited, and most cases are straightforward. Cervical glandular lesions are much less common than squamous lesions, but they result in a disproportionate number of diagnostic problems in both cytological and histological specimens. This book concentrates on cytological and histological aspects of cervical glandular lesions with a complementary chapter on the colposcopy and management of glandular neoplasia. Benign, premalignant and malignant cervical glandular lesions are covered. The former are characterised by a wide range of lesions which may be difficult to distinguish from premalignant and malignant glandular lesions. The full spectrum of premalignant and malignant cervical glandular lesions is expanding with the description of new entities. Although most premalignant and malignant cervical glandular lesions are human papillomavirus (HPV) associated, it is now well established that there are a number of different morphological types of non-HPV-related cervical adenocarcinomas, and these will increase in importance with the reduction in HPV-related cervical preneoplastic and neoplastic lesions secondary to the introduction of HPV vaccination programmes. We have also included chapters on the cytological and histological aspects of uncommon cervical neoplasms which, although rare, result in disproportionate difficulty for the pathologist. Although most lesions can be readily diagnosed using conventional haematoxylin and eosin preparations, immunohistochemistry may provide significant assistance in certain scenarios, and the value of markers is emphasised at relevant points. The majority of the cytology illustrations are photomicrographs of liquid-based cytology preparations reflecting contemporary British, and increasingly international, practice.

It is our hope that this book will be an easy-to-use practical guide which will be of value to consultant and trainee pathologists both specialist and generalist as well as other health care professionals involved in the management of cervical lesions. The many images included to complement the text are all in colour.

Belfast/Sheffield, UK
2014

W. Glenn McCluggage
John H.F. Smith

The Normal Cervix

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John H.F. Smith

Abstract

In this chapter the anatomy and appearance of the normal cervix in histology and cytology specimens will be described with particular emphasis on glandular tissue.

Keywords

Cervix • Endocervix • Squamocolumnar junction • Squamous metaplasia • Transformation zone • Metaplasia

Structure and Development

The cervix is a fibromuscular organ, 3–4 cm in length and approximately 2.5 cm in diameter, lined and covered on the outer aspect by epithelium. It forms the inferior part of the uterus and projects into the vagina. Anatomically it is divided into the portio vaginalis which is that part which projects into the vagina and the supravaginal portion. It is continuous above with the body of the uterus at the uterine isthmus where there is a fibromuscular junction, the internal os, separating the fibromuscular tissue of the cervix from the muscular tissue of the body of the uterus.

The passage between the uterine cavity and the vagina is via the endocervical canal, which is continuous with the endometrial cavity above at the level of the internal os and the vagina below at the external os. The portion of the cervix lying exterior to the external os and in continuity with the vagina is called the ectocervix. The endocervical canal is approximately 3 cm long, fusiform in shape, and flattened from front to back. It measures between 6 and 8 mm in width at the widest point but cyclical changes result in alterations in the dimensions of the canal, in tissue vascularity and in the quantity and biophysical characteristics of mucus secreted by endocervical cells [1, 2]. Mucus secretion with increased vascularity, congestion and stromal oedema predominate during the proliferative phase of the menstrual cycle and reach a peak at ovulation in order to provide an ideal environment for the passage of spermatozoa.

The cervix varies in size and shape depending on a woman's age, parity and hormonal status. In nulliparous women it is barrel-shaped with a small circular external os but it changes shape and size during pregnancy and during delivery and labour, such that the multiparous cervix is larger than that found in nulliparous women and the external os appears as a wide, gaping transverse slit.

W.G. McCluggage et al., *Cellular Pathology of Glandular Lesions and Uncommon Neoplasms of the Cervix*,
DOI 10.1007/978-1-4471-2210-4_1,

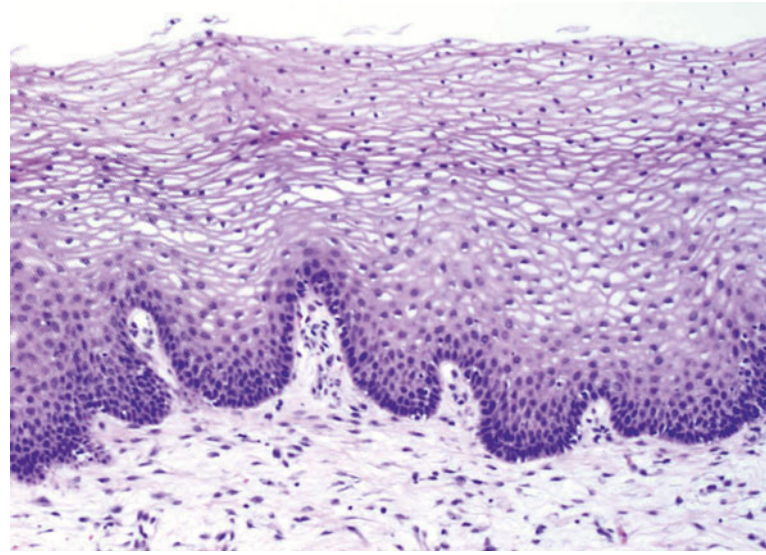

Fig. 1.1 Normal squamous mucosa of the ectocervix

Cervical Epithelium

The cervix is covered by both stratified non-keratinising squamous epithelium and columnar mucin secreting epithelium and these two types of epithelium meet at the squamocolumnar junction.

Squamous Epithelium

The ectocervix is covered by stratified non-keratinising glycogen-containing squamous epithelium. Histologically this epithelium is composed of a basal layer, a parabasal layer, an intermediate cell layer and a superficial cell layer (See Fig. 1.1). It is separated from the underlying cervical stroma by a basement membrane and the epithelial-stromal junction is usually linear but sometimes slightly undulating with short projections of stroma at regular intervals called stromal papillae.

In haematoxylin and eosin stained histological sections basal layer epithelium consists of a single row of small cylindrical cells with relatively large ovoid nuclei and sparse eosinophilic cytoplasm. In normal cervical squamous epithelium the basal layer nuclei maintain a regular perpendicular orientation to the basement membrane. Growth and replacement of the squamous epithelium occurs from the basal layer and therefore nucleoli, numerous chromocentres and mitoses are identified in this layer.

The parabasal cell layer is composed of two or more layers of polyhedral cells with relatively large nuclei and distinct intercellular bridges. Mitoses may be found in this layer particularly in basal hyperplasia in response to chronic infection or trauma.

The intermediate cell layer is composed of polygonal cells with abundant glycogen rich, frequently vacuolated, cytoplasm and small nuclei.

The superficial cell layer is composed of similar cells to those in the intermediate cell layer except that the cells are flattened with even smaller nuclei and evident keratinisation.

Glycogenation of the intermediate and superficial layers is a sign of normal maturation under the influence of oestrogen. In the absence of oestrogen normal maturation does not occur and therefore after the menopause the squamous epithelium of the cervix does not mature beyond the parabasal layer and the epithelium is thin and atrophic.

Columnar Mucin Secreting Epithelium

The endocervical canal is lined by columnar epithelium composed of a single layer of tall slender cells with abundant cytoplasm and basal

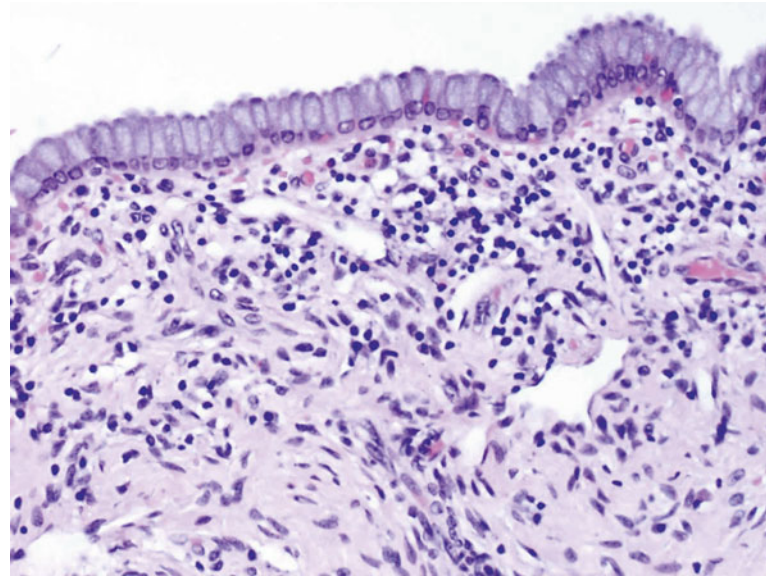

Fig. 1.2 Normal columnar glandular mucosa of the endocervix

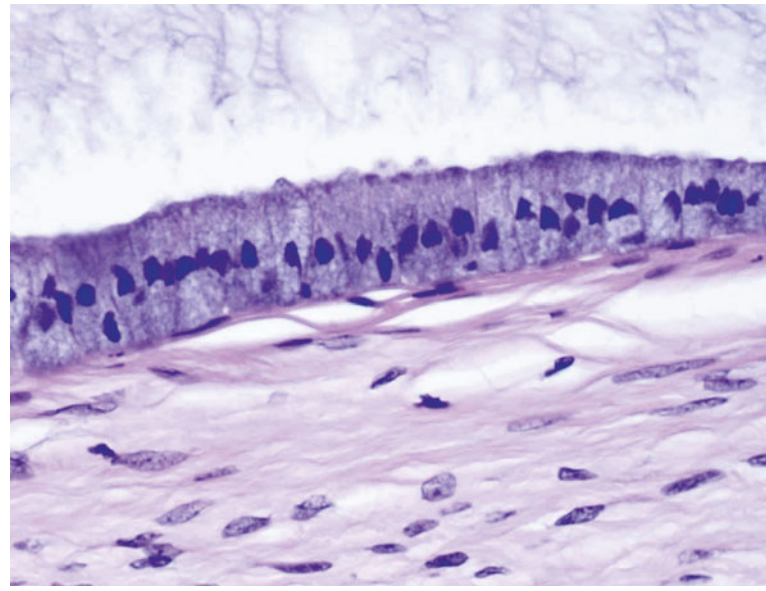

Fig. 1.3 Columnar epithelium of the endocervix with evidence of active secretion. Note the displaced nuclei and intracellular mucin accumulation

situated round or ovoid nuclei (See Fig. 1.2). The nuclei are usually situated in the basal part of the cell but may lie suprabasally or in the middle of the cell during active mucus secretion (See Fig. 1.3).

There are two types of columnar epithelial cell: non-ciliated secretory cells and ciliated cells.

The secretory cells predominate in the columnar epithelium and utilise both apocrine and merocrine secretion to produce both acid and neutral mucin, although the relative amounts vary with the menstrual cycle [3]. The ciliated cells are covered with tiny kinocilia that beat rhythmically towards the cervical canal and vagina. The distribution of the ciliated cells is not uniform in that they are found in highest concentration in the upper endocervical canal close to the endometrial junction and rarely seen close to the squamocolumnar junction (See Fig. 1.4).

The columnar epithelium does not form a single layer of cells lining the endocervical canal. Histological (two-dimensional) examination

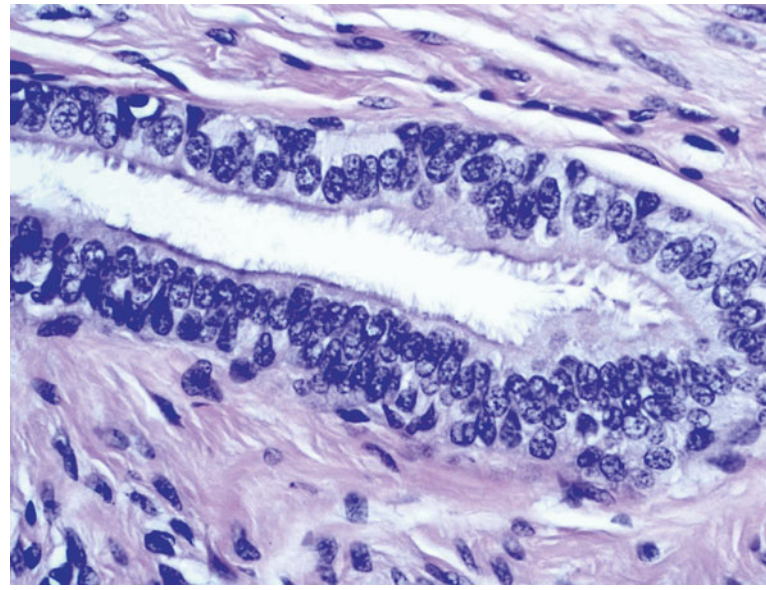

Fig. 1.4 Ciliated columnar cells lining an endocervical crypt in the upper endocervix

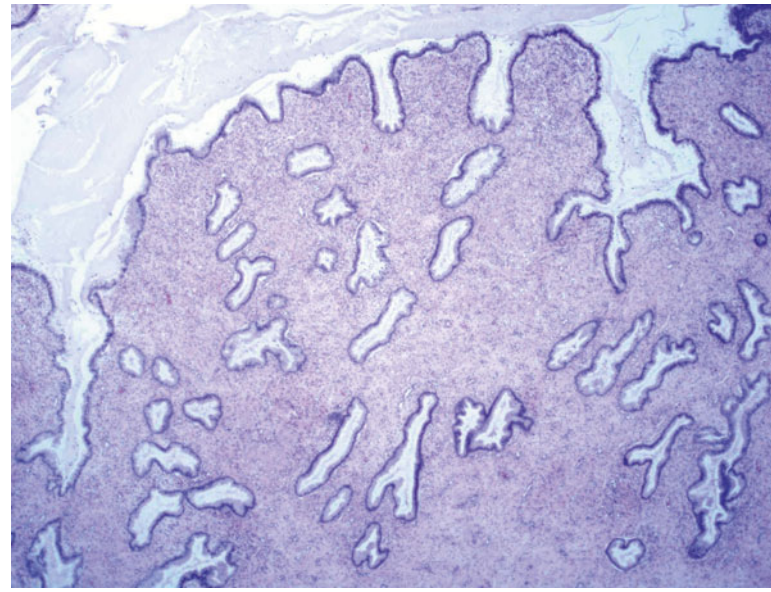

Fig. 1.5 Low power photomicrograph of the endocervix showing the complex crypt architecture

suggests that the endocervical canal is formed of numerous glands lined by columnar epithelium but elegant three-dimensional reconstruction has shown that these apparent glands are in fact a manifestation of an extensive cleft like system whereby there are numerous complex infoldings of endocervical epithelium on stroma to form endocervical folds and crypts [4, 5]. The crypts may extend to a depth of nearly 8 mm from the surface of the endocervical canal and these architectural features may be valuable in the diagnosis of invasive neoplastic lesions of the endocervix (see Chap. 5) (See Fig. 1.5) [6, 7].

Squamocolumnar Junction

The location of the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix in

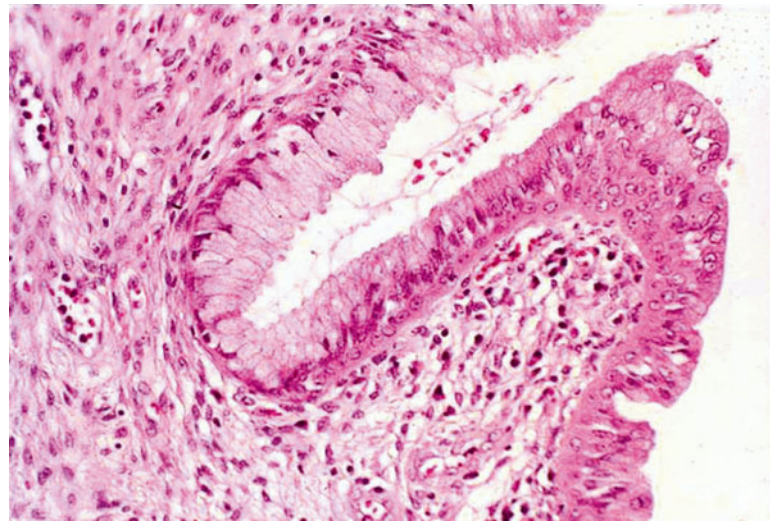

Fig. 1.6 Reserve cell hyperplasia. Initial displacement and replacement of columnar endocervical epithelium by small cuboidal cells

relation to the external os varies over a woman's lifetime and is dependent on hormonal influences, oral contraceptive use and physiological conditions such as pregnancy.

In childhood, the squamocolumnar junction is located at or very close to the external os. After puberty and during pregnancy the cervix swells and enlarges and the endocervical canal elongates under the influence of oestrogen. This leads to eversion of the columnar epithelium of the lower part of the endocervical canal onto the endocervix, a condition called ectropion or ectopy, which is clearly visible on naked eye examination as a prominent glistening red area.

Metaplastic Squamous Epithelium and the Transformation Zone

When the everted columnar epithelium in an ectropion is exposed to the acidic environment of the vagina, the buffer action of the mucus covering the columnar cells is destroyed and the columnar cells undergo metaplastic change and are transformed into squamous epithelium. Squamous metaplasia of the endocervix is a three step process proceeding from reserve cell hyperplasia to immature squamous metaplasia and mature squamous metaplasia.

The first sign of squamous metaplasia is the appearance and proliferation of sub columnar reserve cells, a unicellular layer of small cuboidal cells immediately beneath the normal endocervical columnar cells (See Fig. 1.6). The origin of the reserve cells is uncertain: opinion is divided as to whether they arise from primitive epithelial cells located between the columnar cells in the basement membrane or from sub epithelial stromal or mononuclear cells [8–12].

Progressive growth with stratification of reserve cells results in a multilayered epithelium showing some features of squamous differentiation and replacement of the columnar epithelium by immature squamous epithelium, a process known as immature squamous metaplasia. Immature metaplastic squamous epithelium lacks surface maturation and has inconspicuous intracytoplasmic glycogen in contrast to mature squamous epithelium (See Fig. 1.7).

Eventually the columnar epithelium is entirely replaced by mature squamous epithelium resembling native squamous epithelium and it overlies endocervical crypts (See Fig. 1.8). If endocervical crypt openings are completely occluded mucus accumulates in and expands the crypt to form mucous retention cysts called Nabothian cysts or follicles (See Fig. 1.9). The metaplastic process starts at the original squamocolumnar junction and moves toward the external os through the reproductive period. Thereby a new squamocolumnar junction is formed between the newly formed metaplastic squamous epithelium and the columnar epithelium remaining everted on the ectocervix. In the

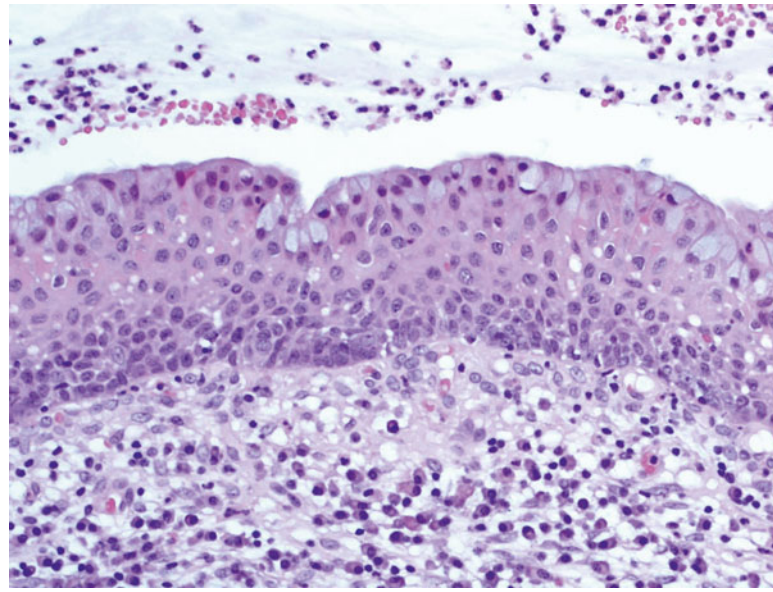

Fig. 1.7 Cervical transformation zone. The surface endocervical epithelium is partly replaced by immature metaplastic squamous epithelium

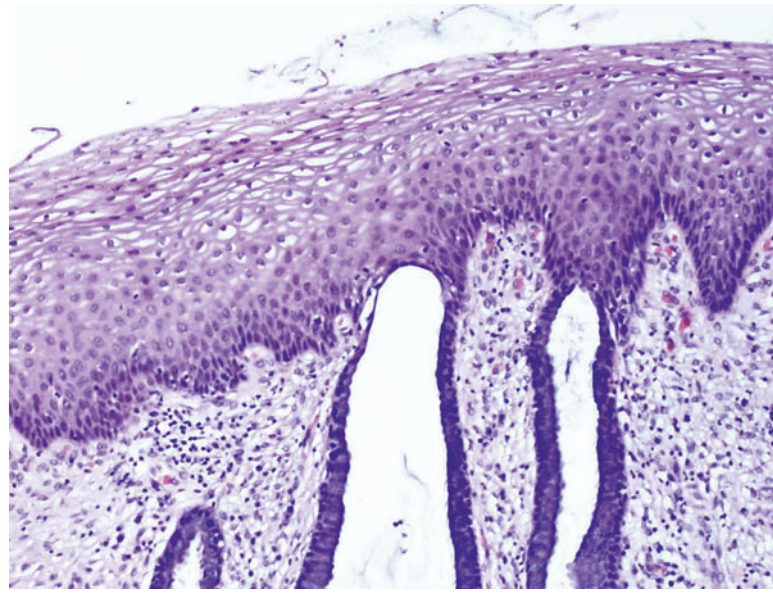

Fig. 1.8 Cervical transformation zone. The surface endocervical epithelium is completely replaced by mature metaplastic squamous epithelium which covers the crypt openings

perimenopausal age range the squamocolumnar junction progressively moves towards the external os and as the cervix shrinks after the onset of menopause due to lack of oestrogen the movement of the new squamocolumnar junction toward the external os is accelerated with the result that the new squamocolumnar junction is often not visible in postmenopausal women on colposcopic examination. Squamous metaplasia is an irreversible process but progresses at varying rates in different areas of the same cervix so that areas of differing maturity may be seen in the metaplastic squamous epithelium associated with residual islands of columnar epithelium. The metaplastic epithelium adjacent to the new squamocolumnar junction is immature whilst that near the original squamocolumnar junction is mature.

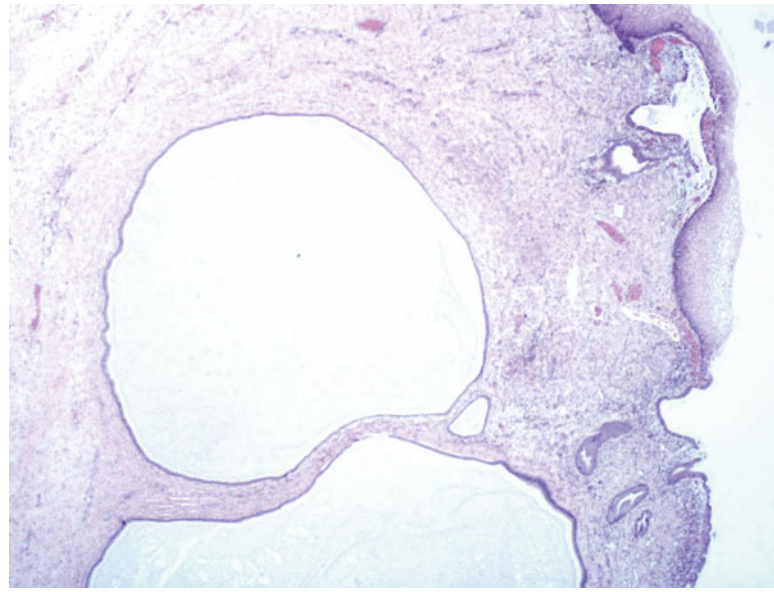

Fig. 1.9 Mucus retention cyst formation in the transformation zone as a result of complete occlusion of crypt openings by metaplastic squamous epithelium

Fig. 1.10 Colposcopic appearance of the cervix in a woman in the reproductive age range showing the original and new squamocolumnar junctions

That part of the cervix where the columnar epithelium has been replaced or is being replaced by metaplastic squamous epithelium is referred to as the transformation zone and is delineated distally by the original squamocolumnar junction and proximally by the new squamocolumnar junction (See Fig. 1.10). It is in this area that oncogenic human papillomaviruses interact with the squamous and glandular epithelium and virtually all squamous neoplasms and the majority of glandular neoplasms of the cervix arise [13–17].

Cytology of Normal Endocervical Epithelium

Normal endocervical cells present in cervical cytology preparations as either cohesive groups or single dispersed cells. The cohesive groups when viewed end on have a characteristic honeycomb appearance with round nuclei, and when viewed in profile form palisades of columnar cells with basal situated ovoid nuclei resembling a “picket fence” (See Figs. 1.11 and 1.12). The individual cells within a cohesive group may show considerable variation in nuclear size but polarity is maintained and they lack other features of neoplasia (See Fig. 1.13). Single cells are recognised by their columnar shape with tall delicate cytoplasm and basal nuclei (See Fig. 1.14). The nuclei of endocervical cells have a fine chromatin pattern and one or more nucleoli may be identified close to the nuclear membrane. Ciliated cells may be identified, particularly in brush samples from the upper endocervical canal as noted above, and must be distinguished from the ciliated cells of tuboendometrioid metaplasia as described in Chap. 6 (See Fig. 1.15).