# Anatomy of the uterine cervix and the transformation zone

The cervix is a fibromuscular organ that links the uterine cavity to the vagina. Although it is described as being cylindrical in shape, the anterior and posterior walls are more often ordinarily apposed. The cervix is approximately 4 cm in length and 3 cm in diameter. The cervix of a parous woman is considerably larger than that of a nulliparous woman, and the cervix of a woman of reproductive age is considerably larger than that of a postmenopausal woman. The cervix occupies both an internal and an external position. Its lower half, or intravaginal part, lies at the upper end of the vagina, and its upper half lies above the vagina, in the pelvic/abdominal cavity (Fig. 2.1). The two parts are approximately equal in size. The cervix lies between the bladder anteriorly and the bowel posteriorly. Laterally, the ureters are in close proximity, as are the uterine arteries superiorly and laterally.

The cervix has several different linings. The endocervical canal is lined with glandular epithelium, and the ectocervix is lined with squamous epithelium. The squamous epithelium meets the glandular epithelium at the squamocolumnar junction (SCJ). The SCJ is dynamic and moves during early adolescence and during a first pregnancy. The *original* SCJ originates in the endocervical canal, but as the cervix everts during these

Fig. 2.1. Line drawing of normal female genital tract anatomy: sagittal section. In this drawing, the uterus is anteverted.
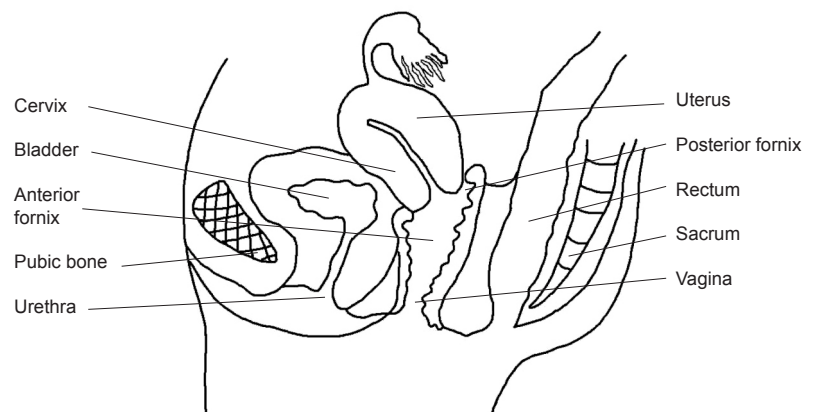
times, the SCJ comes to lie on the ectocervix and becomes the new SCJ. In colposcopy terminology, the SCJ is this *new* SCJ. The epithelium between these two SCJs is the TZ or transition zone, and its position is also variable. It may be small or large and usually becomes more ectocervical during a woman's reproductive years, returning to an endocervical position after menopause.

When the uterus is anteverted, the cervix enters the vaginal vault through a slightly posterior approach, whereby at speculum examination the cervical os is directed towards the posterior vaginal wall (Fig. 2.1). When the speculum is opened, the cervix tends to be brought more centrally into view and into line with the longitudinal axis of the vagina. Most women have an anteverted uterus. When the uterus is retroverted, the cervix tends to enter the vagina slightly more anteriorly, and in this case the cervix may be more difficult to locate at first speculum exposure. When the speculum is positioned properly and opened, the cervix tends to become positioned centrally and in a plane perpendicular to the longitudinal axis of the vagina.

The external os of the cervix will nearly always be visible to the naked eye at speculum examination. The visible external lining of the cervix derives from the vaginal (squamous) epithelium. The endocervical or glandular epithelium is not usually visible to the naked eye at speculum examination. At the upper end of the endocervical canal, the endocervical epithelium becomes the endometrial lining of the uterine cavity. The lower half, or intravaginal part, of the cervix lies at the top of the vagina, surrounded by the vaginal fornices. These are the lateral, anterior, and posterior fornices and are where the vaginal epithelium sweeps into the cervix circumferentially. Squamous cervical cancer accounts for the majority of cervical cancer and originates in the TZ. Glandular cervical cancer originates in either the TZ or the glandular epithelium above the TZ.

2.1 Tissue constituents of the cervix

2.1.1 Stroma

The stroma of the cervix is composed of dense, fibromuscular tissue through which vascular, lymphatic, and nerve supplies to the cervix pass and form a complex plexus.

The arterial supply of the cervix is derived from the internal iliac arteries through the cervical and vaginal branches of the uterine arteries. The cervical branches of the uterine arteries descend in the lateral aspects of the cervix at the 3 o'clock and 9 o'clock positions. The veins of the cervix run parallel to the arteries and drain into the hypogastric venous plexus. The lymphatic vessels from the cervix drain into the common iliac, external iliac, internal iliac, obturator, and parametrial nodes.

The nerve supply to the cervix is derived from the hypogastric plexus. The endocervix has extensive sensory nerve endings, whereas there are very few in the ectocervix. Hence, procedures such as biopsy, thermal coagulation, and cryotherapy are relatively well tolerated in most women, although there is good evidence that local anaesthesia effectively prevents the discomfort of these procedures. Also, the cervix of a parous woman tends to have slightly less sensory appreciation, which may be due to damage to nerve endings during childbirth. Because sympathetic and parasympathetic fibres are also abundant in the endocervix, dilatation and/or curettage of the endocervix may occasionally lead to a vasovagal reaction.
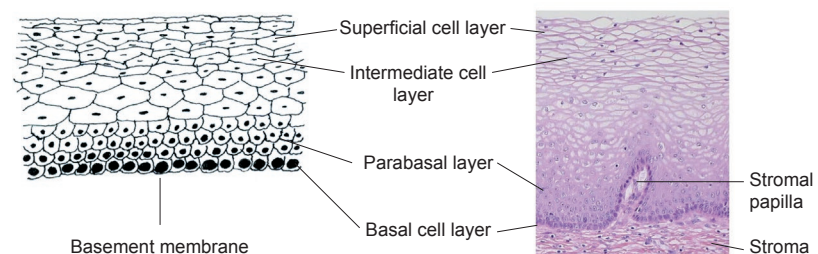
The cervix is covered by both stratified, non-keratinizing squamous epithelium and columnar epithelium. As mentioned above, these two types of epithelium meet at the SCJ.

2.1.2 Squamous epithelium

Usually, most of the ectocervix and the entire length of the vagina is lined with squamous epithelium, which is uniform, stratified, and non-keratinizing. Because mature squamous epithelium contains glycogen, it readily takes up Lugol's iodine (and is therefore Schiller test-negative). When epithelium does not take up Lugol's iodine, it is Schiller test-positive. Cervical squamous epithelium is smooth and looks slightly pink to the naked eye in its non-pregnant state. During pregnancy it becomes progressively more vascular and develops a bluish hue.

The lowest level of cells in the squamous epithelium (Fig. 2.2) is a single layer of round basal cells with large dark-staining nuclei and little cytoplasm, attached to the basement membrane. The basement

Fig. 2.2. Squamous epithelium of the vagina and ectocervix.

Superficial cell layer

Intermediate cell layer

Parabasal layer

Basal cell layer

Basement membrane

Stromal papilla

Stroma

membrane separates the epithelium from the underlying stroma. The epithelial–stromal junction is usually straight. Sometimes it is slightly undulating, with short projections of stroma, which occur at regular intervals. These stromal projections are called papillae, and the parts of the epithelium between the papillae are called rete pegs.

The basal cells divide and mature to form the next few layers of cells, called parabasal cells, which also have relatively large dark-staining nuclei and greenish-blue basophilic cytoplasm. Further differentiation and maturation of these cells leads to the intermediate layers of polygonal cells with abundant cytoplasm and small, round nuclei. These cells form a basket-weave pattern. With further maturation, the superficial layers of large and markedly flattened cells with small, dense, pyknotic nuclei and transparent cytoplasm are formed. Overall, from the basal layer to the superficial layer, these cells undergo an increase in size and a reduction in nuclear size.

The cells in the intermediate and superficial layers contain abundant glycogen in their cytoplasm, which stains mahogany brown or black after the application of Lugol's iodine and magenta with periodic acid–Schiff stain in histological sections. Glycogenation of the intermediate and superficial layers is a sign of normal maturation and development of the squamous epithelium. Abnormal or altered maturation is characterized by a lack of glycogen production.

The maturation of the squamous epithelium of the cervix is dependent on estrogen, and if estrogen is lacking, full maturation and glycogenation do not take place. Hence, after menopause, the cells do not mature beyond the parabasal layer and do not accumulate as multiple layers of flat cells. Consequently, the epithelium becomes thin and atrophic. On visual examination, it appears pale, sometimes with subepithelial petechial haemorrhagic spots, because it is easily prone to trauma.

2.1.3 Columnar epithelium

The endocervical canal is lined with columnar epithelium (often referred to as glandular epithelium). It is composed of a single layer of tall cells with dark-staining nuclei close to the basement membrane (Fig. 2.3). Because of its single layer of cells, it is much shorter in height than the stratified squamous epithelium of the cervix. On visual examination, it appears reddish, because the thin single-cell layer allows penetration of the stromal vascularity. At its distal or upper limit, it merges with the endometrial epithelium in the lowest part of the body of the uterus. At its proximal or lower limit, it meets with the squamous epithelium at the SCJ. It covers a variable extent of the ectocervix, depending on the woman's age and reproductive, hormonal, and menopausal status.

The columnar epithelium does not form a flattened surface in the endocervical canal but is thrown into multiple longitudinal folds protruding into the lumen of the canal, giving rise to papillary projections. It forms several invaginations into the substance of the cervical stroma, resulting in the formation of endocervical crypts (sometimes referred to as endocervical glands) (Fig. 2.4). The crypts may traverse as far as 5–6 mm from the surface of the cervix. This complex architecture, consisting of mucosal folds and crypts, gives the columnar epithelium a grainy or grape-like appearance on visual inspection.

A localized overgrowth of the endocervical columnar epithelium may occasionally be visible as a reddish mass protruding through the external os on visual examination of the cervix. This is called a cervical polyp (Figs. 2.5 and 2.6). It usually begins as a localized enlargement of a single columnar papilla and appears as a mass as it enlarges. It is composed of a core of endocervical stroma

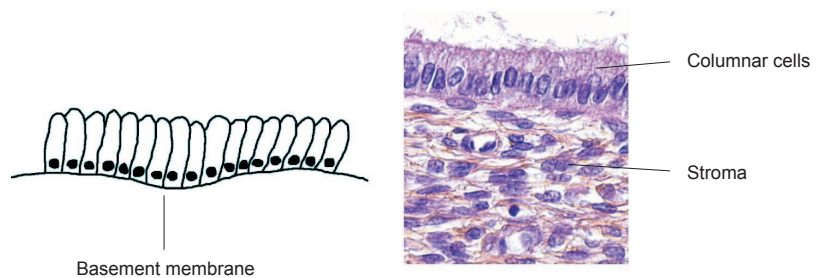**Fig. 2.3.** Columnar epithelium of the endocervical canal.

Columnar cells

Stroma

Basement membrane

Fig. 2.4. Endocervical crypts lined with columnar epithelium.

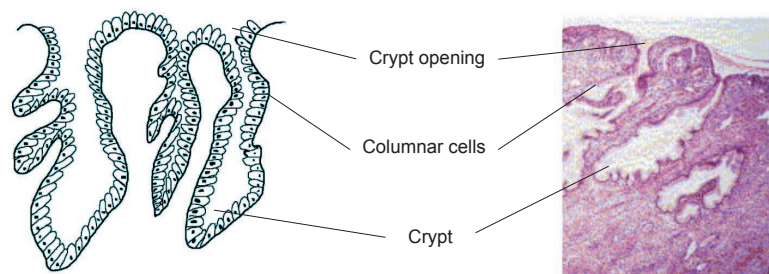Crypt opening

Columnar cells

Crypt

Fig. 2.5. A cervical polyp in the endocervical canal. It is protected from the vaginal environment by abundant mucus in the canal. It is lined with columnar epithelium.
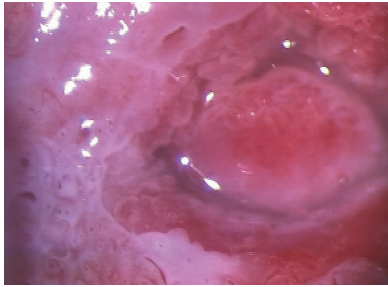

Fig. 2.6. A cervical polyp that has undergone a degree of metaplasia so that it is partially covered by squamous epithelium.
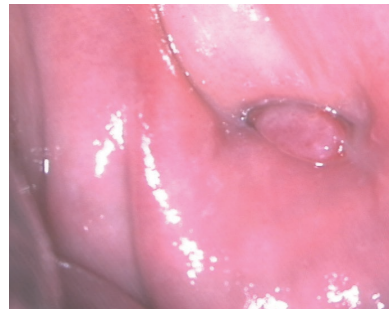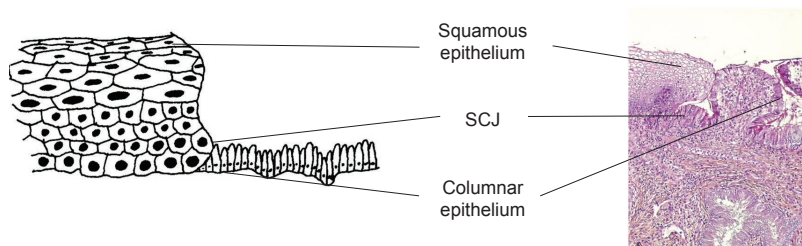

Fig. 2.7. The squamocolumnar junction (SCJ).

lined with columnar epithelium with underlying crypts. Occasionally, multiple polyps may arise from the columnar epithelium. The polyp shown in Fig. 2.5 is lined with columnar epithelium, and it is protected from the metaplastic influence of the vaginal environment by endocervical mucus. The polyp shown in Fig. 2.6 has undergone a degree of metaplasia so that it is partially covered by squamous epithelium.

Glycogenation and mitoses are absent in the columnar epithelium. Because of the lack of intracellular cytoplasmic glycogen, the columnar epithelium does not change colour after the application of Lugol's iodine or remains slightly discoloured with a thin film of iodine solution.

2.1.4 Squamocolumnar junction (SCJ)

The SCJ (Fig. 2.7) sometimes appears as a sharp line with a step, because of the difference in the height of the squamous and columnar epithelium. The location of the SCJ in relation to the external os is variable over a woman's lifetime and depends on factors such as age, hormonal status, birth trauma, use of oral contraceptives, and pregnancy.

The SCJ that is visible during childhood, during perimenarche, after puberty, and in early reproductive life is referred to as the *original* SCJ, because this represents the junction between the columnar epithelium and the *original* squamous epithelium laid down during embryogenesis in intrauterine life. During childhood and around the menarche, the original SCJ is located at, or very close to, the external os (Fig. 2.8).

After puberty and during the reproductive period, the female genital organs develop under the influence of estrogen. Thus, the cervix swells and enlarges and the endocervical canal elongates. This leads to eversion of the columnar epithelium in the lower part of the endocervical canal out onto the ectocervix (Fig. 2.9). This condition is called ectropion or ectopy, which is visible as a strikingly reddish-looking ectocervix on visual inspection (Fig. 2.10). It is sometimes called an erosion or ulcer, which are misnomers. Thus, the original SCJ is located on the ectocervix, far away from the external os (Fig. 2.9). An ectropion may begin or become much more pronounced during pregnancy.

The buffer action of the mucus covering the columnar cells is interfered with when the everted columnar epithelium of an ectropion is exposed to the acidic vaginal environment. This leads to the destruction and eventual replacement of the columnar epithelium by the

Fig. 2.8. Before puberty, the squamocolumnar junction is positioned above and very close to the external os.
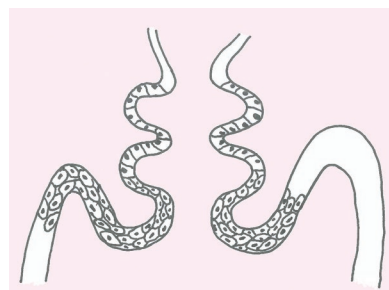

Fig. 2.9. The squamocolumnar junction after eversion of the columnar epithelium out onto the ectocervix, which occurs most commonly during adolescence and early pregnancy.
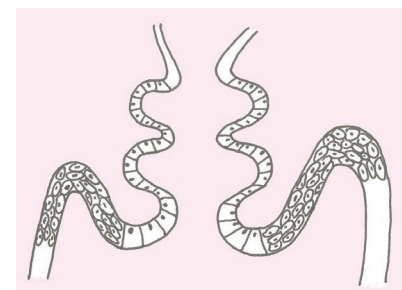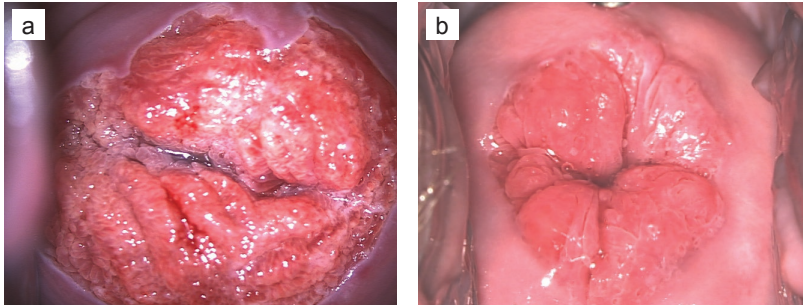
Fig. 2.10. (a) Ectropion with the original squamocolumnar junction (SCJ) situated on the ectocervix. Inside or proximal to this is an area of columnar epithelium. (b) Ectropion with the original SCJ situated on the ectocervix. Inside or proximal to this is an area of columnar epithelium. In this image, the ectropion is beginning to metaplase to squamous epithelium.

newly formed metaplastic squamous epithelium (metaplasia refers to the change or replacement of one type of epithelium by another).

The metaplastic process starts at the original SCJ and proceeds centripetally towards the external os throughout the reproductive period and finally to the menopause. It is also thought that some metaplasia may occur by ingrowth of the squamous epithelium from the squamous epithelium of the ectocervix. Thus, a new SCJ is formed between the newly formed metaplastic squamous epithelium and the columnar epithelium (Fig. 2.11).

As the woman passes from reproductive to perimenopausal life, the new SCJ moves towards the external os (Fig. 2.12). Hence, it is located at a variable distance from the external os, as a result of the progressive formation of new metaplastic squamous epithelium on the exposed areas of the columnar epithelium in the ectocervix. From the perimenopausal period and afterwards, the atrophic cervix shrinks, and consequently, the movement of the new SCJ towards the external os and into the endocervical canal is accelerated. In postmenopausal women, the new SCJ is often invisible on visual examination, because it has become entirely endocervical. The

new SCJ is usually simply referred to as the SCJ.

2.2 Ectropion or ectopy

Ectropion or ectopy is defined as the presence of everted endocervical columnar epithelium on the ectocervix. It appears as a large reddish area on the ectocervix surrounding the external os (Fig. 2.10). The eversion of the columnar epithelium is usually more pronounced on the anterior and posterior lips of the ectocervix, and less so laterally. This is a normal, physiological occurrence. Occasionally, the columnar epithelium extends to the vaginal fornix. The whole mucosa,

including the crypts and the supporting stroma, is displaced in ectropion. It is the region in which physiological transformation to squamous metaplasia occurs, and it is the area that is susceptible to cervical squamous disease.

2.3 Squamous metaplasia

The physiological replacement of the everted columnar epithelium by squamous epithelium is called squamous metaplasia. The vaginal environment is relatively acidic during reproductive life and during pregnancy. The acidity is thought to play a role in squamous metaplasia.

The columnar cells exposed are eventually replaced by metaplastic squamous epithelium. Initially, the irritation of exposed columnar epithelium by the acidic vaginal environment results in the appearance of subcolumnar reserve cells, and these cells proliferate, producing reserve cell hyperplasia, and eventually become metaplastic squamous epithelium.

The reserve cells multiply, differentiate, and eventually lift off the columnar epithelium (Fig. 2.13b and c). The exact origin of the reserve cells is not known.

Fig. 2.11. (a) The incomplete metaplasia that has occurred in the ectocervical columnar epithelium produces a mixed squamous/columnar epithelium in the physiological transformation zone (TZ), lying between the labels a and b in the drawing. (b) The TZ in this image is the area of epithelium (which in this case is normal) between the original squamocolumnar junction (SCJ) and the new SCJ, lying close to the endocervical canal. Gland openings can be clearly seen in a sea of normal mature squamous epithelium in this normal TZ.
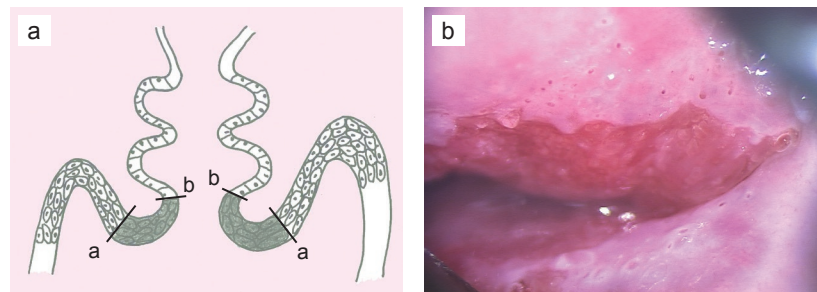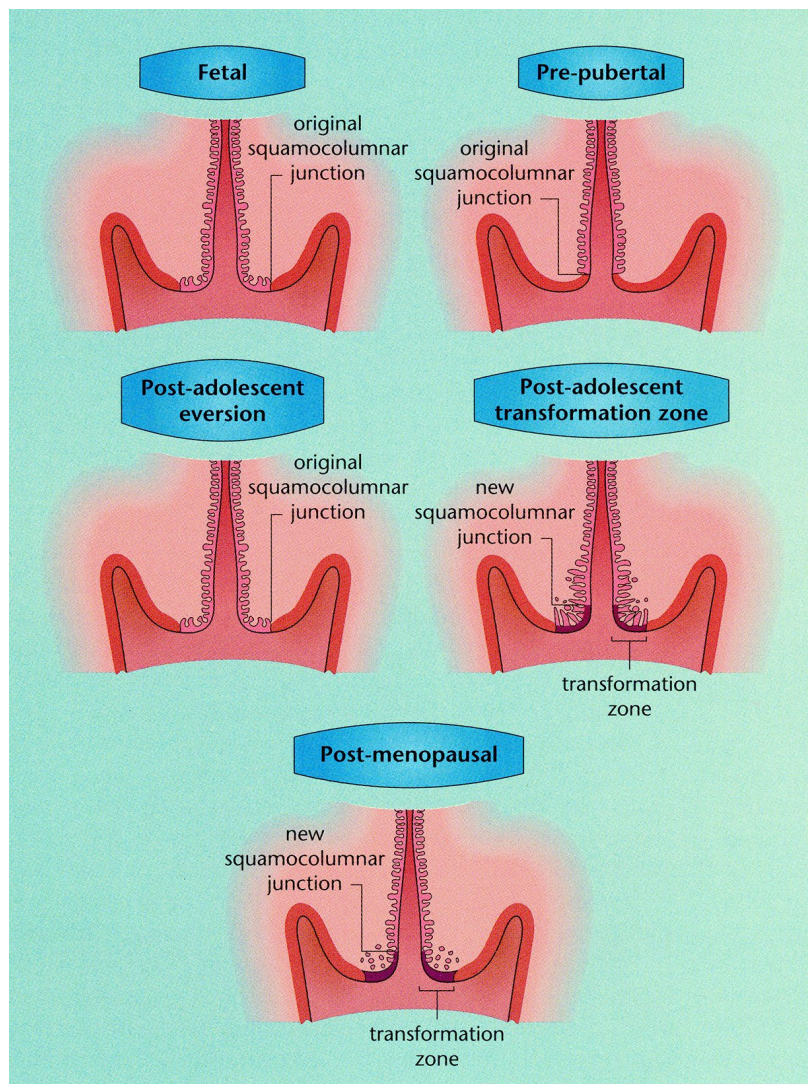
Fig. 2.12. Development of the transformation zone from fetal life to postmenopausal life.

The first sign of squamous metaplasia is the appearance and proliferation of reserve cells (Fig. 2.13a and b). This is initially seen as a single layer of small, round cells with dark-staining nuclei, situated very close to the nuclei of columnar cells, which further proliferate to produce reserve cell hyperplasia (Fig. 2.13b). Morphologically, the reserve cells have a similar appearance to the basal cells of the original squamous epithelium, with round nuclei and little cytoplasm. As the metaplastic process progresses, the reserve cells proliferate and differentiate to form a thin, multicellular epithelium of immature squamous cells with no evidence of stratification (Fig. 2.13c). The term "immature squamous metaplastic epithelium" is used when there is little or no stratification in this thin, newly formed metaplastic epithelium. Immature squamous metaplastic epithelium does not produce glycogen and, hence, does not stain brown or black with Lugol's iodine. Groups of mucin-containing columnar cells may be seen embedded in the immature squamous metaplastic epithelium at this stage.

Numerous continuous and/or isolated fields or foci of immature squamous metaplasia may arise at the same time. It has been proposed that the basement membrane of the original columnar epithelium dissolves and is reformed between the proliferating and differentiating reserve cells and the cervical stroma. Squamous metaplasia usually begins at the original SCJ at the distal limit of the ectopy, but it may also occur in the columnar epithelium close to this junction or as islands scattered in the exposed columnar epithelium.

As the process continues, the immature metaplastic squamous cells differentiate into mature stratified metaplastic epithelium (Fig. 2.13d). For all practical purposes, this resembles original stratified squamous epithelium. Some residual columnar cells or vacuoles of mucus are seen in the mature squamous metaplastic epithelium, which contains glycogen from the intermediate cell layer onward. Thus, the more mature the metaplasia is, the more it will stain brown or black after the application of Lugol's iodine (Fig. 2.14).

Inclusion cysts, also called nabothian follicles or nabothian cysts, may be observed in the TZ in mature metaplastic squamous epithelium (Fig. 2.15). Nabothian cysts are retention cysts that develop as a result of the occlusion of an endocervical crypt opening or outlet by the overlying metaplastic squamous epithelium. The buried columnar epithelium continues to secrete mucus, which eventually fills and distends the cyst. The columnar epithelium in the wall of the cyst is flattened and ultimately destroyed by the pressure of the mucus in it. The outlets of the crypts of columnar epithelium, not yet covered by the metaplastic epithelium,

Fig. 2.13. Development of squamous metaplastic epithelium. (a) The arrows indicate the subcolumnar reserve cells. (b) The reserve cells proliferate. (c) The reserve cells further proliferate and differentiate. (d) Mature squamous epithelium, indistinguishable from native squamous epithelium.

a (40×)

b (20×)

c (10×)

d (10×)

Immature squamous metaplasia

Immature squamous metaplastic epithelium

Mature squamous metaplastic epithelium

Original squamous epithelium
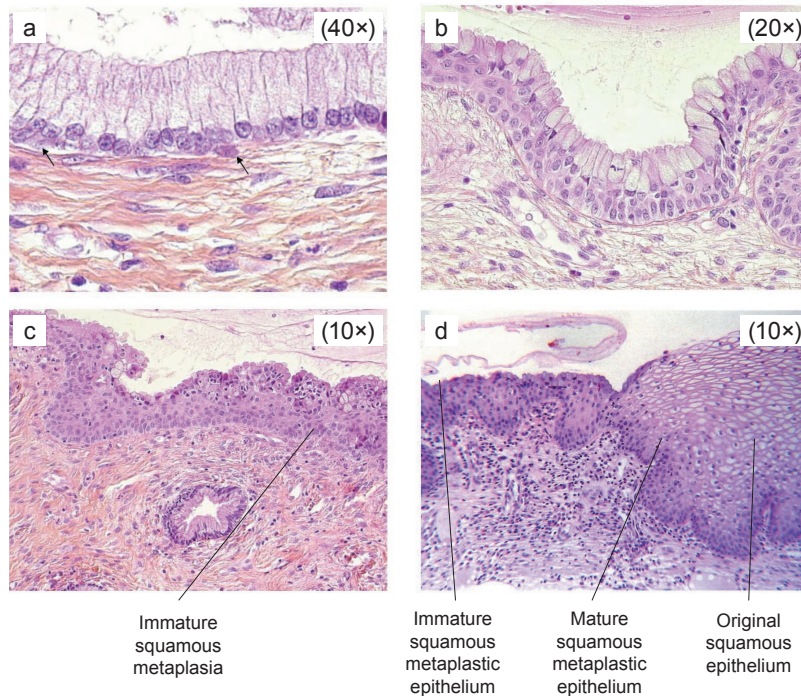
remain as persistent crypt openings (Fig. 2.11b). The farthest extent of the metaplastic epithelium onto the ectocervix can be best judged by the location of the crypt opening farthest away from the SCJ. Fig. 2.16 is a diagrammatic representation of normal TZ tissue components.

Squamous metaplasia is an irreversible process; the transformed epithelium (now squamous in character) cannot revert to columnar epithelium. The metaplastic process in the cervix is sometimes referred to as indirect metaplasia, because the columnar cells do not transform into squamous cells but are replaced by the proliferating subcolumnar cuboidal reserve cells. Squamous metaplasia may progress at varying rates in different areas of the same cervix, and hence many areas of widely differing maturity may be seen in the metaplastic squamous epithelium with or without islands of columnar epithelium. The metaplastic epithelium adjacent to the SCJ is composed of immature metaplasia, and the mature metaplastic epithelium is found near the original SCJ.

Further development of the newly formed immature metaplastic epithelium may take two directions. In the vast majority of women, it develops into mature squamous metaplastic

Fig. 2.14. Uptake of Lugol's iodine in the cervix of a premenopausal woman.

epithelium, which is similar to the normal glycogen-containing original squamous epithelium for all practical purposes. In a very small minority of women, an atypical, dysplastic epithelium may develop. Certain oncogenic HPV types may infect the immature basal squamous metaplastic cells and, rarely, turn them into precancerous cells. The uncontrolled proliferation and expansion of these atypical cells may lead to the formation of an abnormal dysplastic epithelium, which may regress to normal, persist as dysplasia, or progress to invasive cancer after several years, depending on whether the HPV infection is allowed to become a transforming infection (see Chapter 4).

2.4 Transformation zone (TZ)

The TZ is that area of epithelium that lies between the native and unaffected columnar epithelium of the endocervical canal and the native squamous epithelium deriving from the vaginal and ectocervical squamous epithelium (Fig. 2.17).

The eversion of endocervical epithelium from inside the endocervical canal onto the outside of the cervix, i.e. the ectocervix, takes place at variable times and rates, but

Fig. 2.15. A nabothian follicle is seen at the 7 o'clock position in this image of a normal transformation zone. There is a little light reflection seen at its tip.

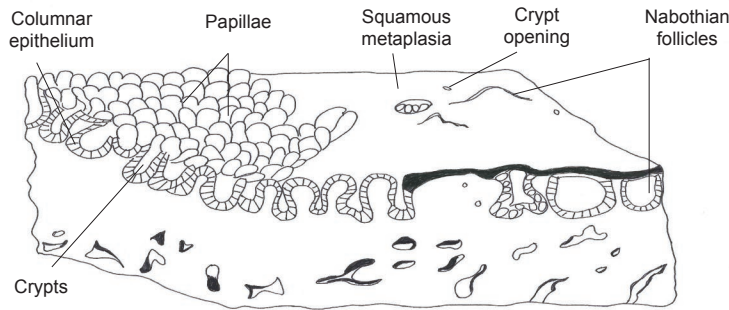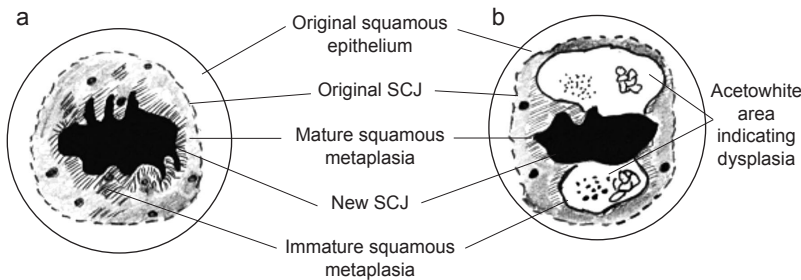**Fig. 2.16.** Epithelial components of the transformation zone.

Fig. 2.17. (a) Schematic diagram of the normal transformation zone. (b) Schematic diagram of the abnormal or atypical transformation zone harbouring dysplasia. SCJ, squamocolumnar junction.

generally speaking it occurs during adolescence and during a first pregnancy (Fig. 2.12). As a result, the columnar epithelium on the ectocervix is exposed to the relatively acidic vaginal environment and undergoes squamous metaplasia, producing the physiological TZ, as described above. This process, when complete, probably results in protection from HPV infection, but during this process the dynamic TZ is susceptible to HPV infection, whereby it may infect the basal layers of the epithelium in the TZ and, in a small proportion of cases, initiate the development of CIN (Fig. 2.18). Why this dysplastic epithelium develops in some women and not in others is currently uncertain, but it is associated with oncogenic HPV types in 99% of cases. Most people will be infected with oncogenic HPV types early on in their normal sexual life, but the great majority will clear the infection without consequence (see

Chapter 4). When the TZ becomes abnormal or atypical, it is called the atypical TZ. The components of the TZ are also depicted in Fig. 2.16.

The TZ varies in its size and its precise position on the cervix, and it may lie partially or completely in the endocervical canal. Where it is and how visible it is determine its type

(see Annex 1). In most women of reproductive age, the TZ is of type 1, and the magnified and light-illuminated view afforded by colposcopy will usually present the colposcopist with a clear view of all the components of the TZ as well as the native squamous epithelium and the native and untransformed columnar epithelium of the endocervical canal (Fig. 2.16). Occasionally (in about 4% of cases), the examination will reveal a so-called original or congenital TZ, as depicted in Fig. 2.19.

2.4.1 Congenital transformation zone

During early embryonic life, the cuboidal epithelium of the vaginal tube is replaced by the squamous epithelium, which begins at the caudal end of the dorsal urogenital sinus. This process is completed well before birth, and the entire length of the vagina and the ectocervix is normally covered by squamous epithelium. This process proceeds very rapidly along the lateral walls, and later in the anterior and posterior vaginal walls. If the epithelialization proceeds normally, the original SCJ will be located at the external os at birth. If this process is arrested for some reason, or incomplete, the original

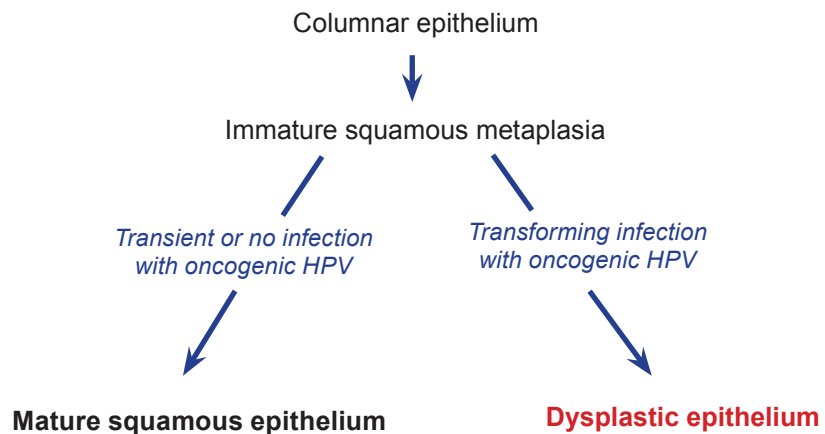**Fig. 2.18.** Effect of infection with oncogenic HPV on immature squamous epithelium.
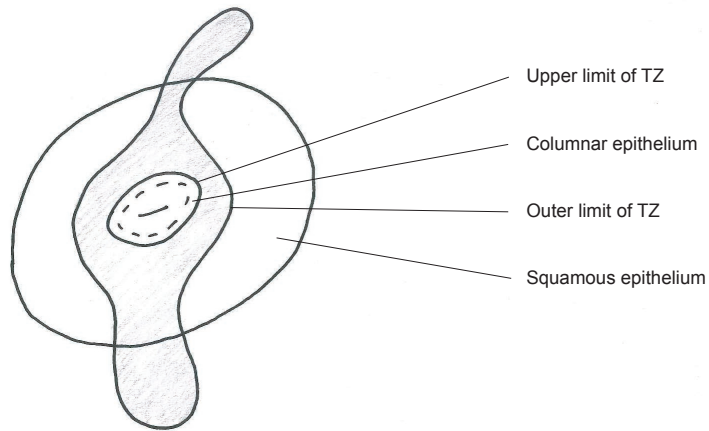
Fig. 2.19. The typical congenital or original transformation zone (TZ).

Upper limit of TZ

Columnar epithelium

Outer limit of TZ

Squamous epithelium

SCJ will be located distal to the external os or may rarely be located on the vaginal walls, particularly involving the anterior and posterior fornices. The cuboidal epithelium remaining here will undergo squamous metaplasia. This late conversion to squamous epithelium in the anterior and posterior vaginal walls, as well as the ectocervix, results in the formation of the congenital TZ. Thus, it is a variant of intrauterine squamous metaplasia in which differentiation of the squamous epithelium is not fully completed because of an interference with normal maturation. Excessive maturation is seen on the surface (as evidenced by keratinization), with delayed, incomplete maturation in deeper layers. Clinically, it may be seen as an extensive whitish-grey, hyperkeratotic area extending from the anterior and posterior lips of the cervix to the vaginal fornices. Gradual maturation of the epithelium may occur over several years. This type of TZ is seen in fewer than 5% of women and is a variant of the normal TZ.

Key points

- The cervix enters the vagina anteriorly or posteriorly depending on its version.

- The position of the original squamocolumnar junction moves during periods of relatively high circulating estrogen levels.

- The exposed everted columnar epithelium will metaplase over time to become mature glycogen-laden squamous epithelium, which stains iodine-positive (Schiller test-negative).

- The transformation zone is where squamous cervical cancer originates.

- The transformation zone is an area of partially squamous, partially columnar, and partially metaplastic epithelium, which lies between the original and new squamocolumnar junctions.