Squamous Metaplasia

Squamous metaplasia is a **replacement of normal endocervical epithelium by squamous epithelium** of varying degrees of maturity. This is a very frequent event that may be confined to a small area of the endocervix or may be very extensive and involve the **surface epithelium and the glands.**

Squamous metaplasia is a **normal, physiological event** during maturation of the female genital tract, notably in the epithelium of the transformation zone.

Pathogenesis

Electron microscopic studies, notably by Bonilla-Musoles and Barbera (1970) and by Philipp (1975), documented that the small **basal or reserve cells** of the endocervical epithelium have the dual potential of differentiating either into mucus-producing normal endocervical cells or into squamous cells, a view confirmed by Tsutsumi et al (1993). It is likely that **hormones,** notably estrogens, play a role in the origin of squamous metaplasia. However, because squamous metaplasia is often observed in biopsy material from cervices showing chronic inflammation, it has also been linked to **inflammatory processes.** Squamous metaplasia is also observed in the presence of intrauterine contraceptive devices and, therefore, may be a **reaction to mechanical pressure.** The precise mechanisms leading to squamous metaplasia must still be elucidated. There may be some **analogy between squamous metaplasia and the events occurring in the formation of the epidermis,** as proposed by Sun et al (see Chap. 2). Sun documented that the transformation of a simple cuboidal epithelium into mature epidermis of the skin is accompanied by a sequential activation of keratin genes of ever higher molecular weights . Still, keratin polypeptides in metaplastic epithelium appear to be unique and differ from cytokeratins normally present in the squamous epithelium of the cervix and those found in the endocervical epithelium (Gigi-Leitner et al, 1986).

Histology

The earliest stages of squamous metaplasia can be identified as a focus of multiplication of the basal cells of the endocervical epithelium. As these small cells grow towards the surface and become larger, their **cytoplasm becomes eosinophilic and homogeneous** . The glandular epithelium may remain on the surface while the underlying squamous epithelium forms increasingly mature cells. In most cases, however, the glandular surface epithelium is cast off and the endocervical epithelium is replaced by squamous epithelium that may be either **mature, resembling the squamous epithelium of the vagina,** or **immature,** composed of **smaller squamous cells of intermediate or parabasal type** (Fig. 10-4B). The term *immature*, as used here, should not be confused with a malignant process. Various stages of transition between normal endocervical epithelium and mature metaplastic squamous epithelium may be observed. By special stains, **mucus may nearly always be demonstrated** in the cytoplasm of the metaplastic cells, indicating close relationship to the endocervical epithelium. Squamous metaplasia may replace the endocervical mucosa lining the **endocervical canal** or **endocervical glands.** Squamous metaplasia of endocervical glands may be discrete and focal, or diffuse. In extreme cases, one or several glands may be filled with squamous epithelium. If the metaplastic squamous epithelium is **immature, the finding may mimic a neoplastic process,** as discussed below under atypical metaplasia.

Cytology

Only immature squamous metaplasia can be identified in cytologic material because cells derived from mature metaplasia cannot be distinguished from normal squamous cells. Squamous metaplasia of the endocervical mucosa can be diagnosed **with certainty in cervical smears** if flat sheets of **polygonal parabasal squamous cells with** Within the sheets, the metaplastic squamous cells usually form **clearly visible cell borders.** One surface of the sheets is often **flattened,** corresponding to the surface of the metaplastic epithelium. Occasionally, the clusters of metaplastic cells are **loosely structured** and are composed of **angulated squamous cells**. On close inspection, the distinct **flattening of the surface** of the cluster is evident and sometimes there are transitions toward well-formed, mucusproducing columnar endocervical cells.

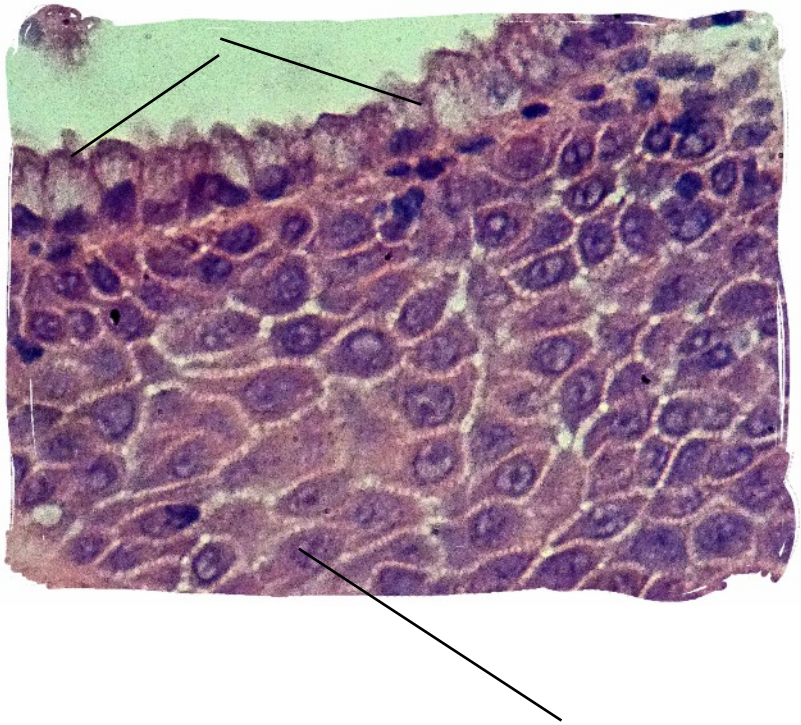
The **cytoplasm** of the metaplastic cells is either **basophilic or eosinophilic** and may show **fine vacuoles** in which **mucus** can be demonstrated by special stain. Occasionally, the vacuoles can be large and may be **infiltrated with polymorphonuclear leukocytes.** The **nuclei** of the metaplastic cells are spherical, measuring on the average 8 µm in diameter, but may be larger. Within the nuclei, small **chromocenters and occasionally tiny nucleoli** may be observed. Rarely, **small spindly keratinized cells** with slender pyknotic nuclei may originate from the surface of squamous metaplastic epithelium.

Unfortunately, **metaplastic cells in their classical configuration in sheets are not always present in cell preparations, particularly those collected in a liquid medium and subsequently dispersed.** In such preparations, the **parabasal metaplastic squamous cells occur singly** and are usually characterized by **irregular, polygonal configuration with cytoplasmic processes, or spikes,** as commonly observed in parabasal cells removed from their epithelial setting. The **cytoplasmic processes are an artifact** occurring during smear preparation by **extensions of the cytoplasm at points of desmosomal junctions** with adjacent cells. As the cells are being separated during smear preparation, the solid desmosomes resist rupture better than the elastic cytoplasm, which, as a consequence of mechanical stretching, becomes elongated at points of junction. Occasionally, one surface of these cells is flat, corresponding to the lining of the endocervical canal.

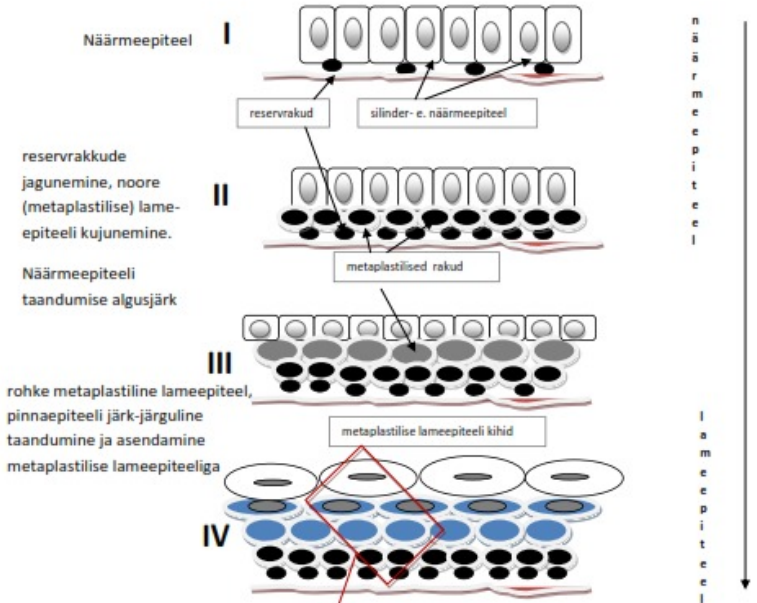
As has been discussed in Chapter 8, the mere **presence of parabasal squamous cells in a cervicovaginal smear is not diagnostic of metaplasia.** Such cells may originate from the squamous epithelium of the vagina or the cervix under a variety of circumstances unrelated to metaplasia. The term **metaplastic cells** that has been suggested for parabasal cells, while picturesque, is not always scientifically sound.

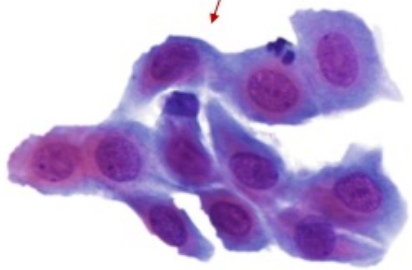
Several attempts have been made to distinguish metaplastic cells from parabasal cells derived from native squamous epithelium by identification of keratins of various molecular weights. Thus, keratins 15, 16 and, occasionally, keratin 6 were observed in endocervical reserve cells and in squamous metaplasia (Smedts et al, 1993) whereas positive stain for keratin 17 was found useful in the differentization of metaplastic cells from normal parabasal cells (Martens et al, 1999). Still, **if angulated parabasal cells are trapped in the endocervical mucus or if the sample has been removed directly from the transformation zone or the endocervical canal by an instrument, such cells may be considered as adequate evidence that the smear is representative of the endocervical epithelium undergoing squamous metaplasia.** The information on the value of such findings in liquid preparations as evidence of smear adequacy is not available.

pindmiselt säilunud näärmeepiteel



metaplastilised lameepiteelirakud
histoloogilises preparaadis

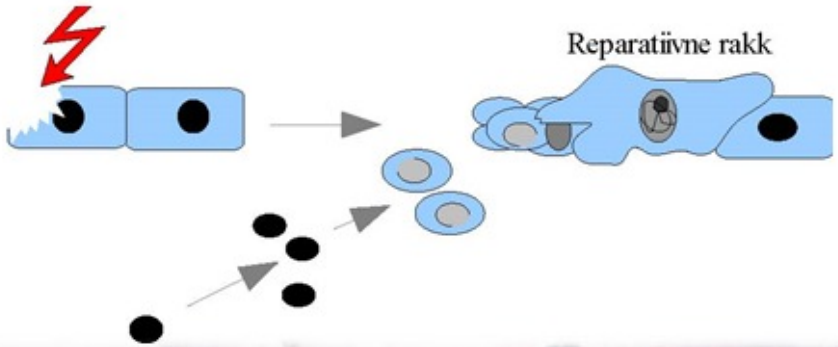


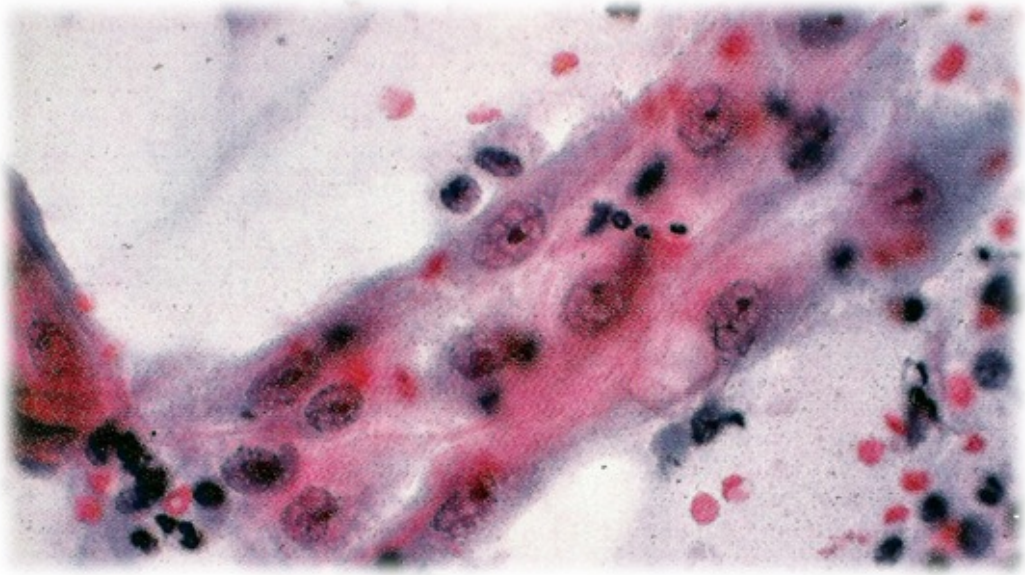


metaplastilised lameepiteelirakud
tsütoloogilises preparaadis

Reparatsioon on kahjustatud koe, surnud rakkude asendamine uute vastsünteesitud rakkudega (haava paranemine). Protsess teostub reservrakkude intensiivse jagunemise teel, mille tulemusena valmib noor reparatiivne epiteel

Probleem: nähtusega võib kaasneda rakuline atüpism (atüüpiline reparatsioon)





Tsütoloogia:

Reparaiivne rakk esindab noort ebaküpset epiteeliliiki. Rakukuju nurgeline, vahel piklik-ovaalne; võivad esineda tsütoplasma jätkelised väljasopistused; rakutuum eba-proportsionaalselt suurenenud.

Tuum: võrkjas, hõreda kromatiinsubstantsiga hele tuum, tuumakesi üks kuni mitu ning tuleb sageli ette hulgituumsust.

Kohaldatav diagnoos: NILM

REPAIR (FLORID SQUAMOUS METAPLASIA)

The term **repair** has been introduced into the field of gynecologic cytology by Bibbo et al (1971) and by Patten (1978). These authors described atypical cells of endocervical and squamous origin with a number of abnormal cytoplasmic and nuclear features in patients with recent past history of radiotherapy to the uterine cervix, recent hysterectomy, other clinical procedures, such as cautery or biopsy, past history of severe cervicitis (Bibbo et al, 1971), and "partial or complete destruction (of the epithelium) by infection and inflammation" (Patten, 1978). Thus, this is a very heterogeneous group of patients wherein many different factors may account for the cellular abnormalities. Most important, perhaps, histologic evidence of true repair of a damaged epithelium (i.e., epithelial regrowth over a defect) has not been provided by Bibbo and to a very limited extent by Patten.

The **concept of repair** is valid but only under well-defined circumstances, for example, after a conization of the uterine cervix or other documented form of epithelial injury. In the histologic material, **tongues of poorly formed, young epithelial cells bridging the defect caused by prior surgery may be observed** (Fig. 10-9A). The mechanisms of "repair" or healing of a wounded epithelium are extremely complex (Singer and Clark, 1999) and have not been studied in the uterine cervix but probably resemble those in the skin.

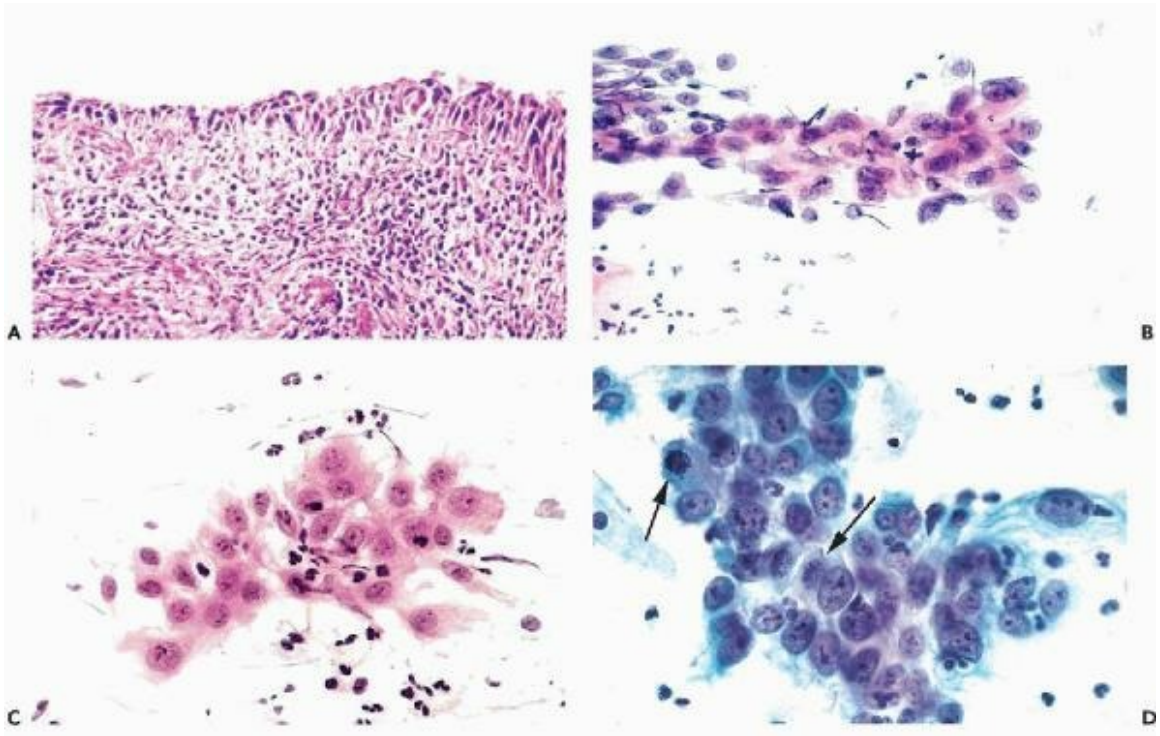


Figure 10-9 "Repair." *A.* The appearance of the cervical epithelium 4 days after a cone biopsy. The surface is lined by small, atypical epithelial cells. *B.* A sheet of epithelial cells from the same patient showing marked variability in sizes and configuration, corresponding to the young epithelium lining the surface of the cervical defect. *C.* Irregular flat sheets of endocervical or metaplastic cells showing prominent nucleoli. *D.* A cluster of endocervical cells showing marked variability in nuclear sizes and prominent nucleoli. Mitotics figure are present (*arrows*).

Cytology

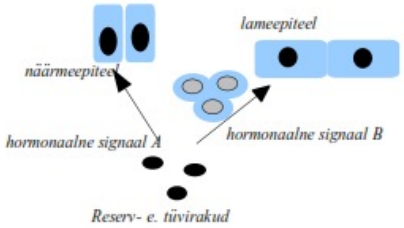
A smear obtained approximately 1 week after a procedure damaging the cervical epithelium may show some rather **characteristic cytologic features.** The smears show **flat sheets, composed of tightly fitting cells, generally resembling metaplastic cells** (Fig. 10-9B,C). The cells may **vary in size** and their cytoplasm may be vacuolated and infiltrated with polymorphonuclear leukocytes. Occasionally, the cells may show **bizarre, sometimes elongated configuration.** The **nuclei** of these cells also **vary in size, may show some degree of hyperchromasia, and, most importantly, contain one or more clearly visible nucleoli of variable sizes. Mitotic figures can be observed** (Fig. 10-9D). There are usually **few, if any, single cells** with similar characteristics. The background of the smear usually shows a great deal of fresh blood and inflammation.

The manifestations of repair may be particularly **difficult to interpret in smears of postmenopausal women with epithelial atrophy.** The nuclei of the epithelial cells are enlarged, of uneven sizes, and hyperchromatic, mimicking malignant lesions. Because the thin epithelial lining offers little protection, bundles of spindly cells representing cervical stroma, may be present. We observed such cells after cervical biopsies, conization, or energetic curettage.

"Repair" reaction may occur **after surgical procedures,** as illustrated above, **as a reaction to chronic inflammatory events** or in the presence of a **foreign body or object in the endocervical canal.** For example, **intrauterine contraceptive devices** or **endocervical polyps** may be the cause of such abnormalities (see below). There remain, however, a number of patients in whom similar cell abnormalities may be observed in smears **in the absence of any known events that could account for the "repair."** It is likely that, in such patients, the cell abnormalities represent an **exuberant or florid squamous metaplasia** of the endocervical epithelium.

Kokkuvõtteks:

Metaplaasia on koe teisenemine. Antud juhul vaatleme metaplaasiat epiteeelkoe näitel, milles näärmeepiteel diferentseerub e. teiseneb lameepiteeliks. See toimub sageli vastava hormonaalse mõjutuse tulemusena ning günekoloogilises sfääris kohtab seda nähtust naissuguhormoonide kontsentratsiooni muutuste korral. Põhjustesks näit. a): rasedus, b): perimenopaus, c): ravimi toime (kontratseptiivid), väikestes piirides toimub epiteeli ümberteisenemine ka d): menstruatsioonitsükli käigus.



Protsess toimub reservrakkudes toimuva „ümberlülituse" tulemusena, peale mida hakkab temast arenema teine epiteelilik

Epiteeli teisenemine ei toimu aga üleöö ning vaheastmetena eksisteerivad ebaküpsed (noored), lõpuni diferentseerumata epiteelirakud, mida tsütoloogilises uuringumaterjalis tuvastatakse metaplastiliste rakkudena.

Metaplaasia bioloogiline tähendus: Epiteeli ümberkohandumie muutunud oludega, ehk adaptatsioon.

Reparatsioon on kajustatud koe, surnud rakkude asendamine uute vastsünteesitud rakkudega (haava paranemine). Protsess teostub reservrakkude intensiivse jagunemise teel, mille tulemusena valmib esmalt noor küpsemata reparatiivne epiteel