

DYSPLASTIC EPITHELIUM

Invasive cervical cancer is usually preceded by a long phase of cellular atypia, collectively referred to as cervical intraepithelial neoplasia (CIN). Pre-cancerous lesions of the cervix have different terminology (Figure 83): cervical intraepithelial neoplasia (CIN) (Richart CIN grading), cervical dysplasia (Reagan WHO) or squamous intraepithelial lesions (SIL) (Bethesda System). CIN is further categorized into

grades 1, 2 and 3 whereas dysplasia is divided into three groups: mild, moderate and severe. The Bethesda System (TBS) has created the term squamous intraepithelial lesion (SIL) which comprehends low-grade (L-SIL) and high-grade (H-SIL) lesions. HPV lesions and CIN 1 are included in L-SIL whereas CIN 2, CIN 3 and in situ carcinoma (ISC) belong to high-grade SIL.

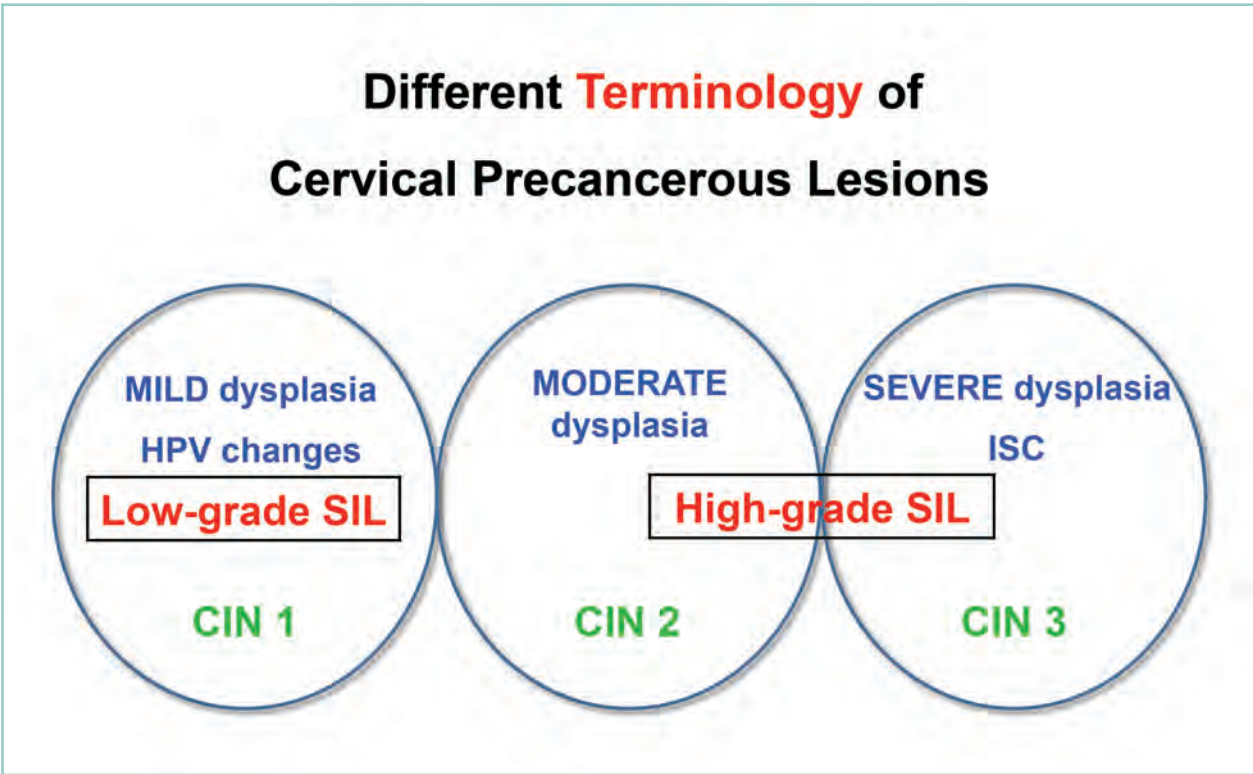


Figure 83 - Different terminology of cervical precancerous lesions.

The behavior of squamous metaplasia holds the key to the understanding of cervical oncogenesis.

During the immature metaplastic change, epithelium may attain exposure to a mutagenic agent and may become abnormal. Human papillomavirus (HPV) is the major infectious etiological agent that is associated with the development of pre-cancerous lesions of the cervix.

In low-grade CIN, most of the atypical protein-rich cells are located in the lower third of the epithelium where acetic acid can not penetrate. Acetowhitening is delayed and less intense compared to high-grade CIN or early invasive carcinoma. The acetowhite epithelium associated with low-grade CIN is more dense, thick and opaque compared to areas with immature metaplastic epithelium and turns white more quickly. Acetowhite lesions associated with CIN point away from the external os and spread centrifugally.

In high-grade lesions and preclinical invasive cancer a large number of dysplastic cells, abnormally loaded in nucleoproteins, reach the superficial layers of the epithelium (Figure 84). After acetic acid treatment, the direct light is quickly reflected by the dense ep-

ithelium, giving an opaque, grey-white (Figure 85) or snow-white appearance (Figure 86). The acetowhite change quickly appears and persists for more than one minute. These lesions usually have regular and well-defined margins which may sometimes be raised and rolled-out.

High-grade dysplastic epithelium a shows more or less complete absence of maturation of the cell layers and disappearance or very marked decrease of glycogen content. Consequently, the application of Lugol's iodine solution will give a mustard or saffron yellow color (Figure 87). High-grade lesions that do not stain with iodine are known as positive Schiller's test or iodine negative areas.

Iodine staining is a must before performing biopsy or ablative procedures, to ensure free margins of the healthy mucosa. It should be pointed out that Schiller's test is extremely useful in the evaluation of all the vaginal folds and above all in the presence of iodine-negative areas that have shown faint acetowhitening. Furthermore, iodine staining is helpful for novel colposcopists in order to localize abnormal areas and confirm the colposcopic suspicion. Nevertheless, many colposcopists have stopped Schiller's

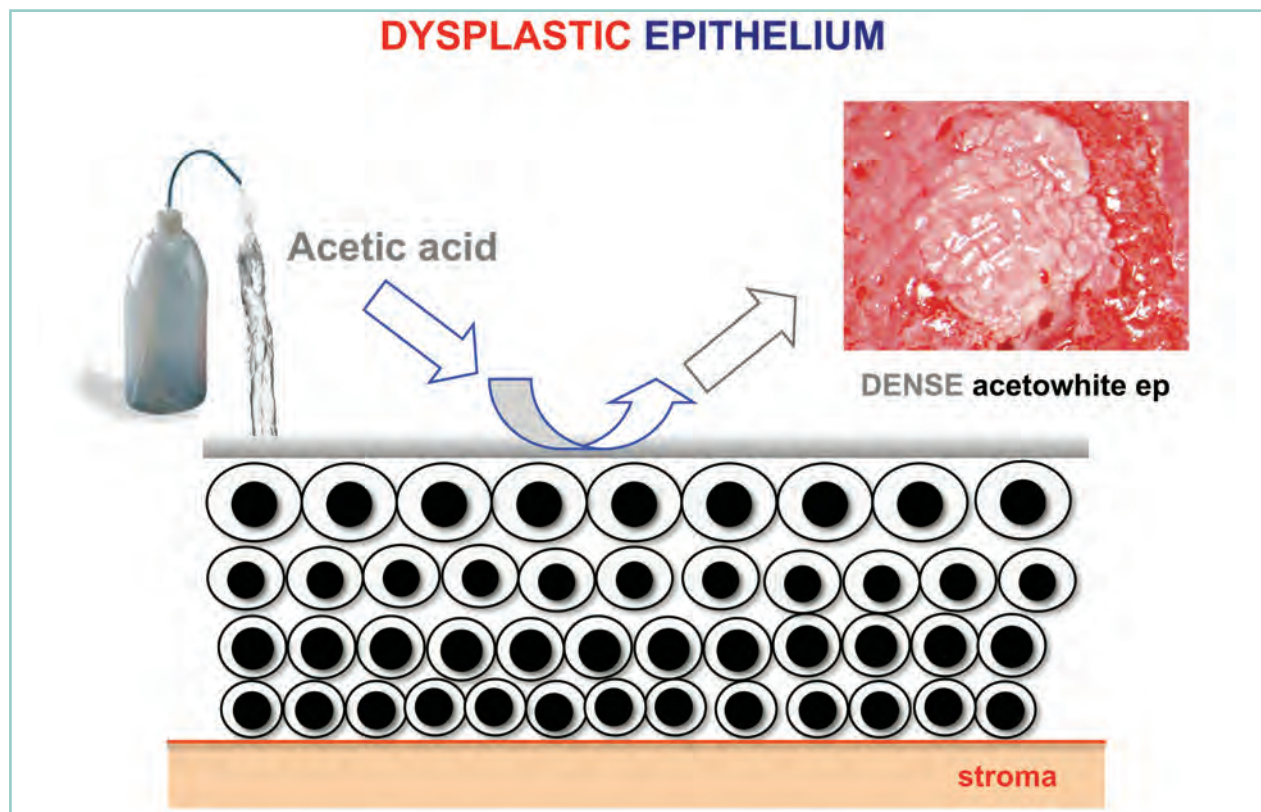


Figure 84 - Diagrammatic representation of the light pathway, through a dysplastic epithelium, after application of acetic acid. The cervix in the colpophotograph shows a dense acetowhite epithelium.

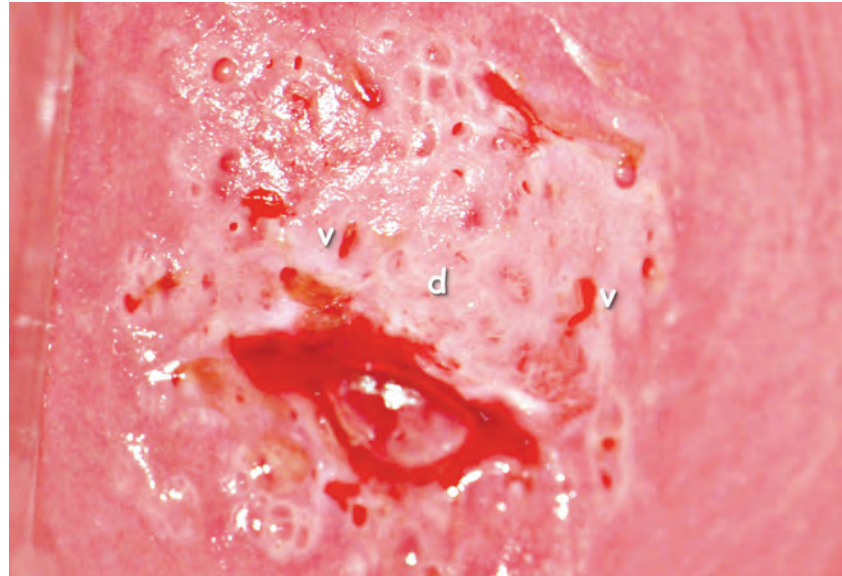


Figure 85 - Dense acetowhite epithelium (d), with atypical vessels that appear and disappear abruptly (v). Histology revealed this lesion to be CIN 3/ISC.

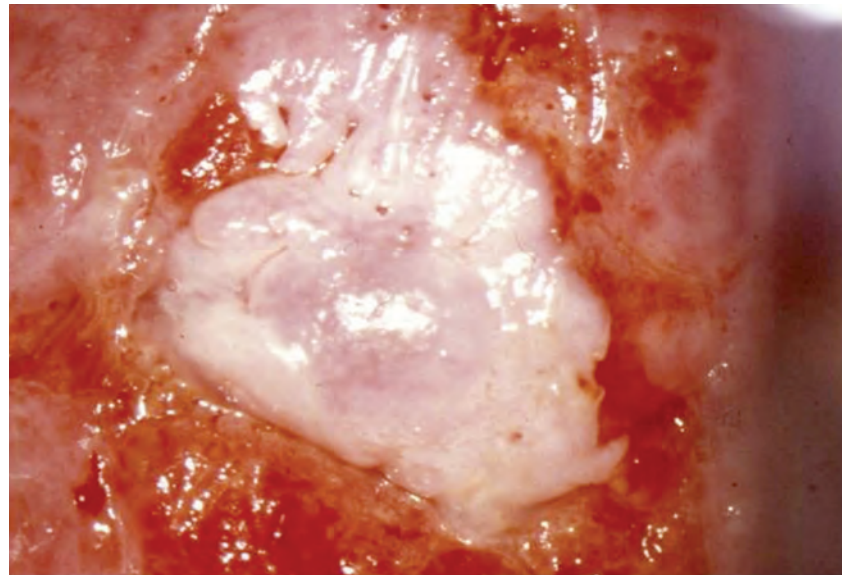


Figure 86 - Dense acetowhite lesion with snow-white appearance (CIN 3).

test, considering it a non-specific test that does not add further information to the colposcopic evaluation. Furthermore, iodine staining may obscure very minute vascular details and it is often difficult to differentiate between atrophic mucosa lacking in glycogen and iodine-negative dysplastic areas. Additionally, possible cervical trauma caused by insertion of the vaginal speculum may result in an iodine negative-area.

Acetowhite lesions may be associated with characteristic vascular patterns such as punctuation and/or mosaic. Changes in vascular patterns are closely related to histologic changes.

In an atypical transformation zone, dysplastic epithelium starts to grow in buds or blocks. Due to

the dysplastic process, the nutritional requirements of the tissue increases, and individual stromal papillae do not become flatter but instead are broadened, elongated and more irregular in size and shape. They sometimes lift the epithelium, giving a micropapillary or warty appearance. A thin layer of epithelium remains on top of the capillaries that may be trapped within the elongated stromal papillae. These histologic abnormalities occurring in the atypical transformation zone are essential for the understanding of punctate and mosaic patterns. Punctuation and mosaic patterns may be classified as either fine or coarse.

Capillaries within stromal papillae may undergo dilatation and proliferation near the surface, where

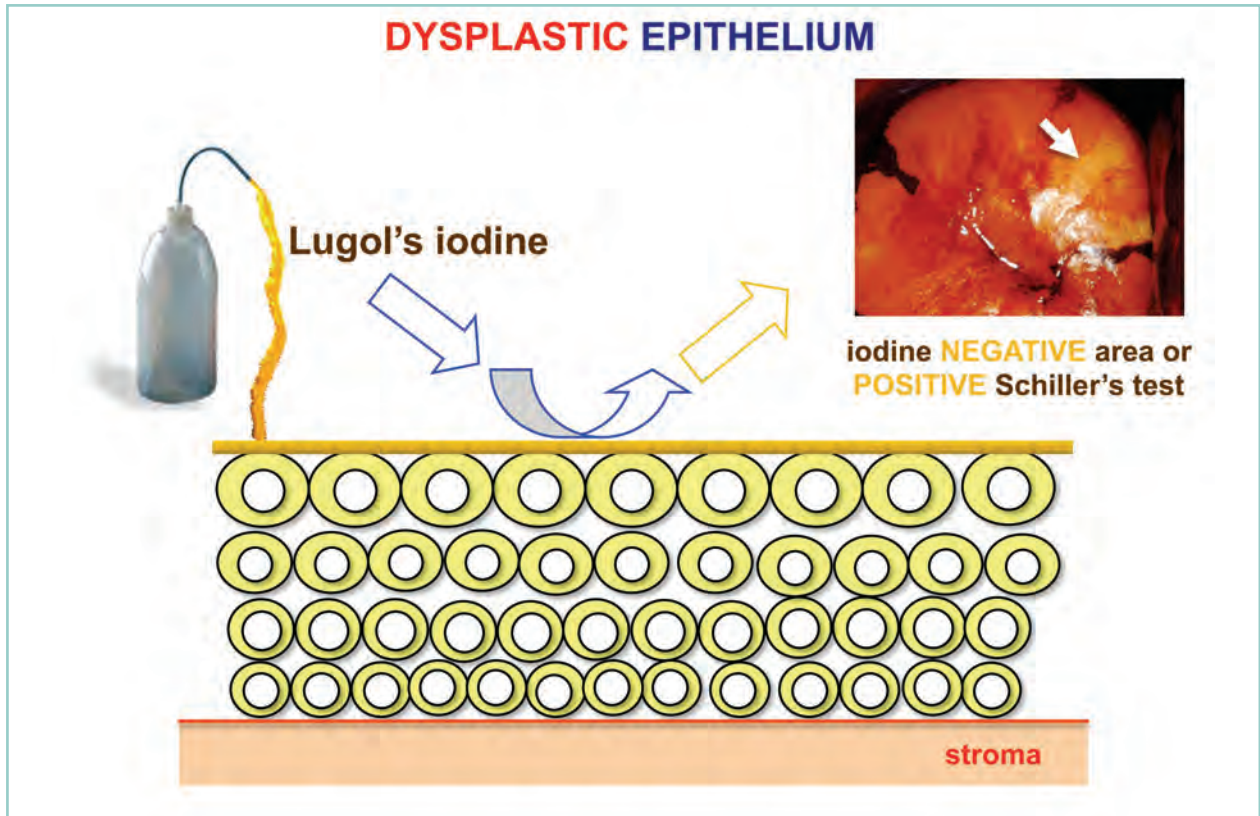


Figure 87 - Diagrammatic representation of the light pathway, through a dysplastic epithelium, after Lugol's iodine application. The colposcopic photograph displays an iodine negative area (arrow).

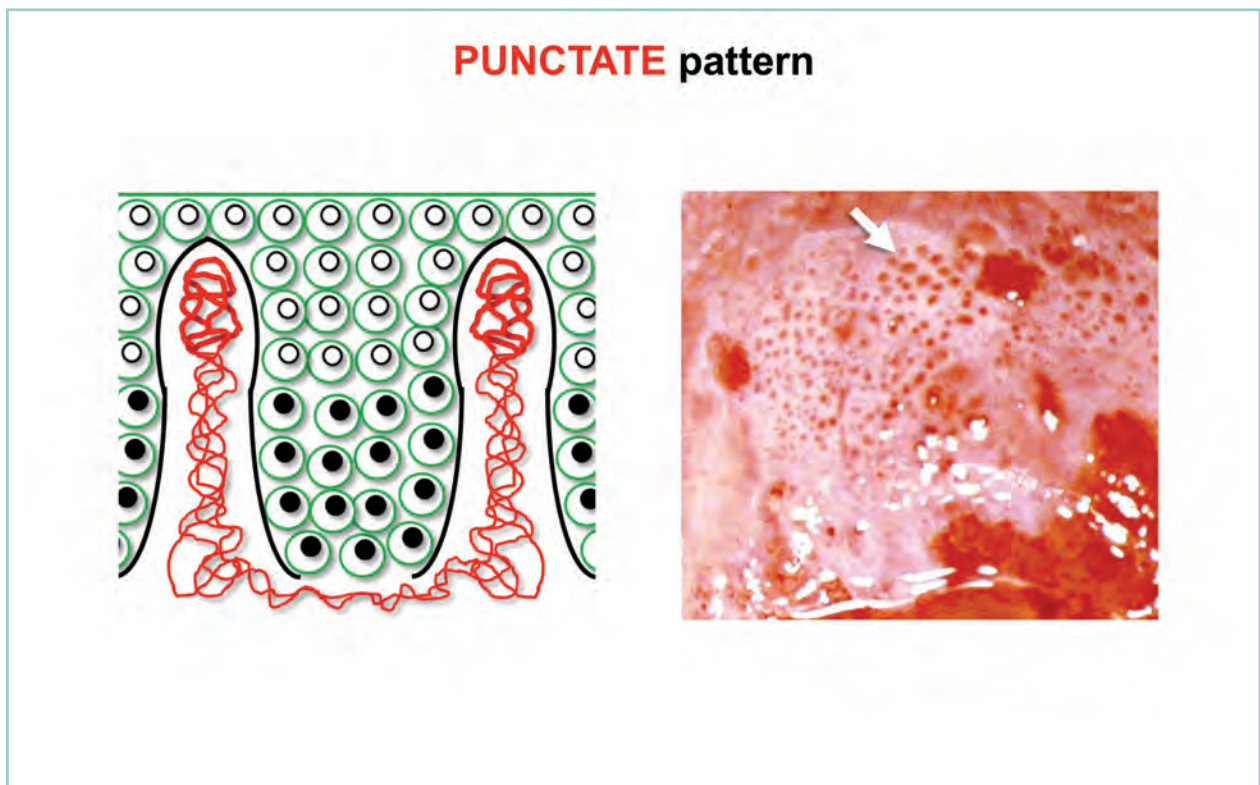


Figure 88 - Diagrammatic representation and colposcopic photograph of punctate pattern. The arrow indicates a coarse punctation with irregular intercapillary distance (CIN 3).

Table 1 - 2011 IFCCP Nomenclature - Accepted in Rio World Congress, July 5, 2011
(Nomenclature Committee chairman: Jacob Bornstein MD)

2011 IFCCP colposcopy terminology of the cervix			
General assessment		<ul style="list-style-type: none"> • Adequate/inadequate for the reason ... (i.e.: cervix obscured by inflammation, bleeding, scar) • Squamo-columnar Junction visibility: completely visible, partially visible, not visible • Transformation zone types 1,2,3 	
Normal colposcopic findings		Original squamous epithelium: <ul style="list-style-type: none"> • Mature • Atrophic Columnar epithelium <ul style="list-style-type: none"> • Ectopy Metaplastic squamous epithelium <ul style="list-style-type: none"> • Nabothian cysts • Crypt (gland) openings Deciduous in pregnancy	
Abnormal colposcopic findings	General principles	Location of the lesion: Inside or outside the T-zone, Location of the lesion by clock position Size of the lesions: Number of cervical quadrants the lesion covers, Size of the lesion in percentage of cervix,	
	Grade 1 Minor	Thin aceto-white epithelium Irregular, geographic border	Fine mosaic Fine punctuation
	Grade 2 (Major)	Dense aceto-white epithelium Rapid appearance of acetowhitening, Cuffed crypt (gland) openings	Coarse mosaic, Coarse punctuation, Sharp border, Inner border sign Ridge sign
	Non specific	Leukoplakia (keratosis, hyperkeratosis), Erosion Lugol's staining (Schiller's test): stained/non-stained	
Suspicious for invasion		Atypical vessel Additional signs: Fragile vessels, Irregular surface, Exophytic lesion, Necrosis, Ulceration (necrotic), tumor/gross neoplasm	
Miscellaneous finding		Congenital transformation zone, Condyloma, Polyp (Ectocervical/endocervial) Inflammation,	Stenosis, Congenital anomaly, Post treatment consequence, Endometriosis

they are seen in a stippled pattern as red dots on a white or opaque background after application of acetic acid. This atypical architecture gives rise to so-called *punctuation* (Figure 88).

Punctuation may be fine or coarse (2011 IFCCP Nomenclature) (Table 1), based on the intercapillary distance and the size of dilated vessels which reflect the severity of the lesion. In *fine* punctuation, the

delicate dots are close together (Figure 89), whereas in *coarse* punctuation petechiae are larger and widely separated (Figure 90).

As has been mentioned, a fine punctuation arranged in radiating lines from the external os (healing lines) may be seen in metaplastic maturation or neovascularization occurring in a healing process (Figure 45). Low-grade SIL produces intermediate

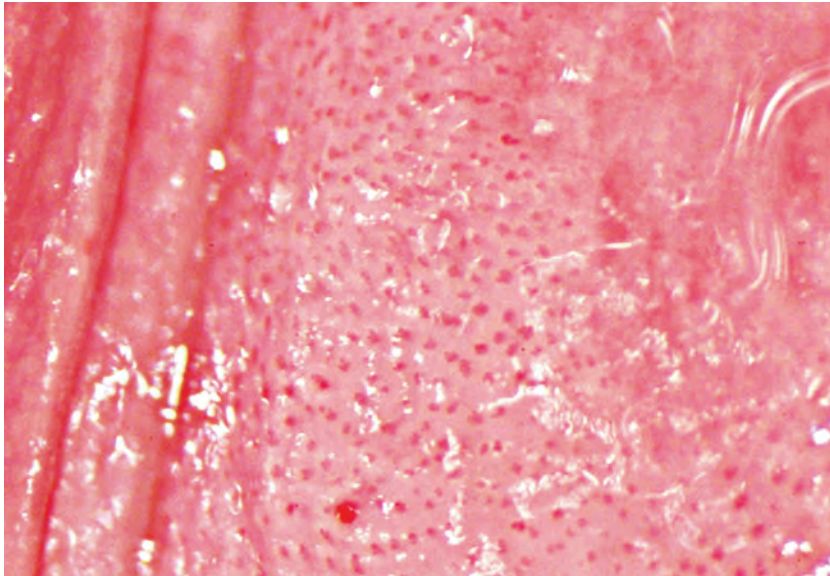


Figure 89 - Fine punctation pattern showing fine dots with regular intercapillary distance.

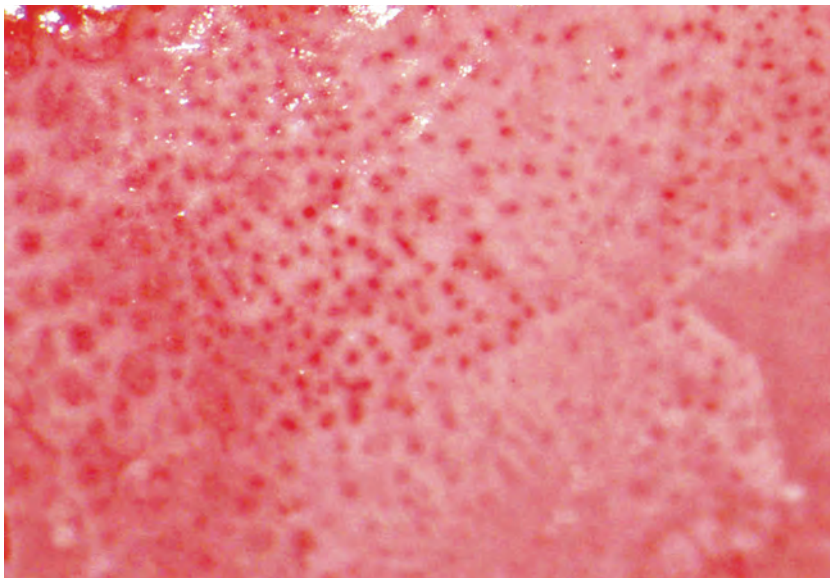


Figure 90 - Coarse punctation with large, widely separated petechiae.

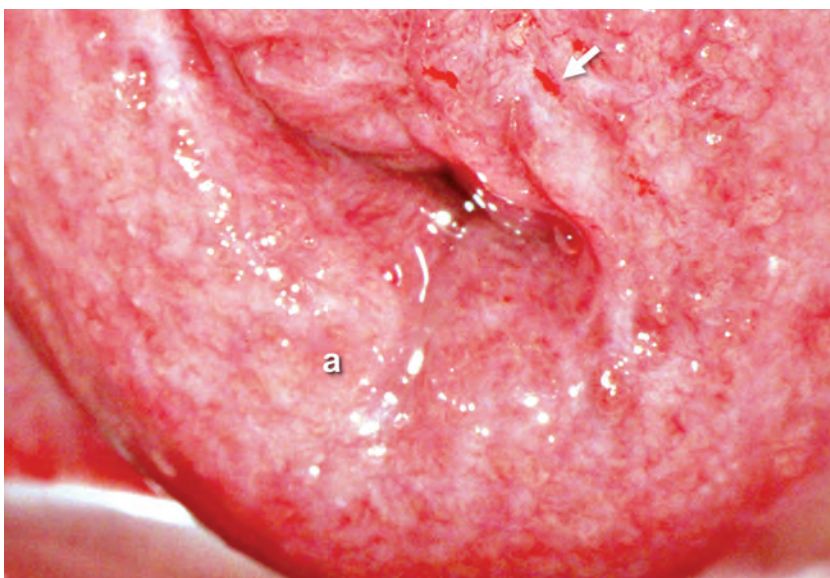


Figure 91 - Capillary effusions (arrow) and diffuse faint acetowhitening are due to an inflammatory condition.

forms of punctation, with varying degree of intercapillary distance, so that sometimes it is difficult to classify the punctate as fine or coarse.

Widespread fine punctation (Figure 80), capillary effusions (Figure 91) or diffuse dilated hairpin capillaries (Figures 92, 93) are generally observed diffusely across the ectocervix in inflammatory conditions. Often these capillaries are clustered in patches, scattered on the cervix (Figure 94), vagina (Figure 95) and vulva (Figure 96), or they can involve the whole vestibulum (Figure 97). These capillaries lie close together, without any sharp border between normal and abnormal epithelium. In the presence of inflammation, these numerous red spots covering the cervix and vagina vary in shape and distribution, and are due to patchy infil-

tration of the stroma, associated with dilated capillaries.

Patched capillaries and vascular effusions may also be observed in presence of severe dystrophy in menopause or in pharmacologically induced conditions (Figure 98). Direct microscopy may assist in reaching a correct diagnosis, displaying an atrophic cell pattern characterized by basal and parabasal, without any evidence of inflammation (Figure 99). Fine or coarse punctation may be also observed in association with respectively low-grade and high-grade anal intraepithelial neoplasia (AIN) (Figure 100).

In histologic abnormalities, punctation is usually confined in a well-delimited area, sharply separated from normal epithelium. In high-grade lesions,

Figure 92 - Inflammation produces dilated capillaries and fine punctation.

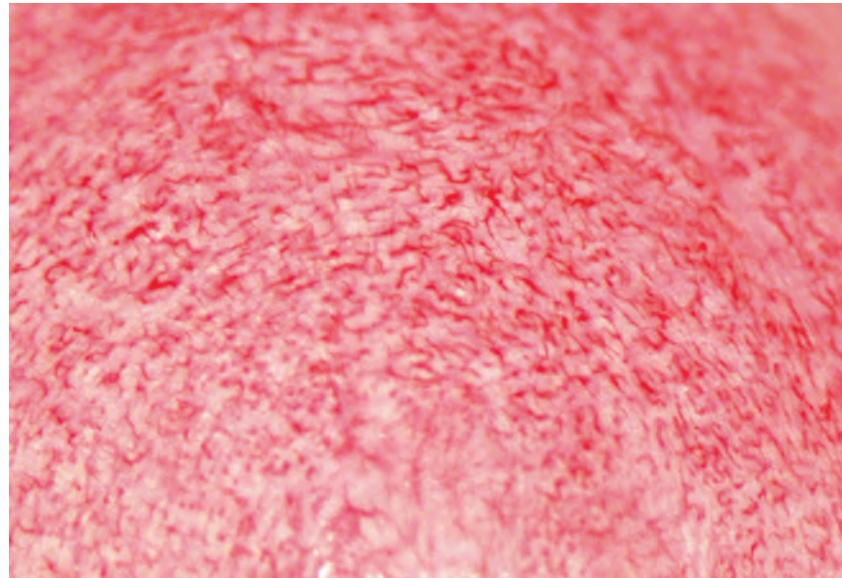
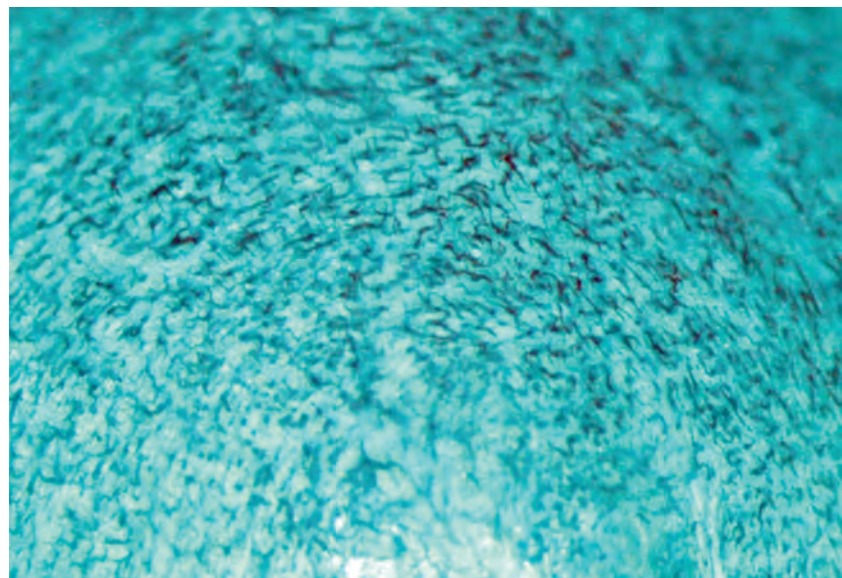


Figure 93 - Saline colposcopy view of the previous case, with the aid of a green filter.



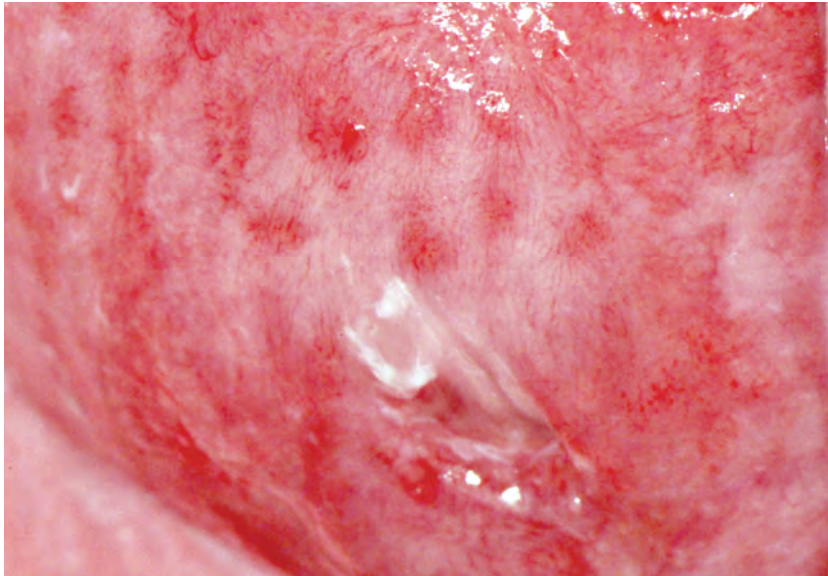


Figure 94 - Patched capillaries, scattered on the cervix. Direct microscopy revealed *Candida* infection.

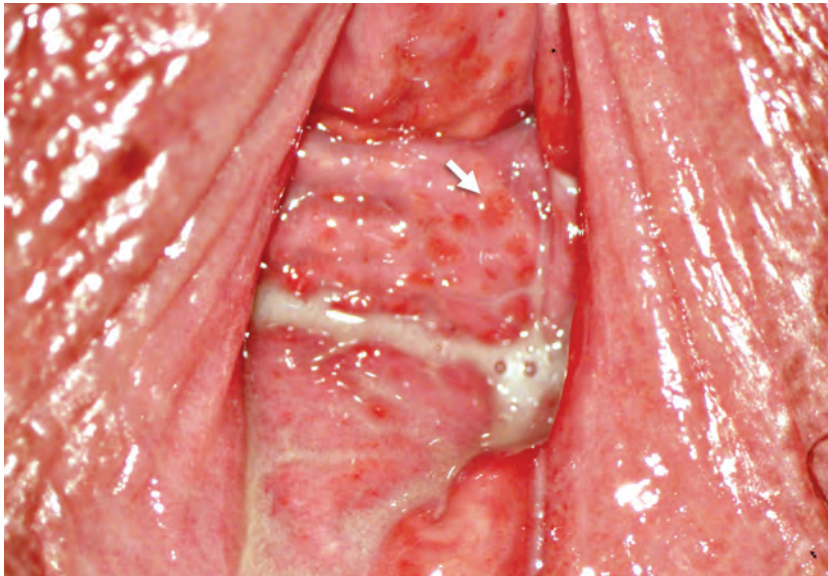


Figure 95 - Patches of dilated capillaries involve the vaginal walls, due to an infection by *Trichomonas vaginalis*.

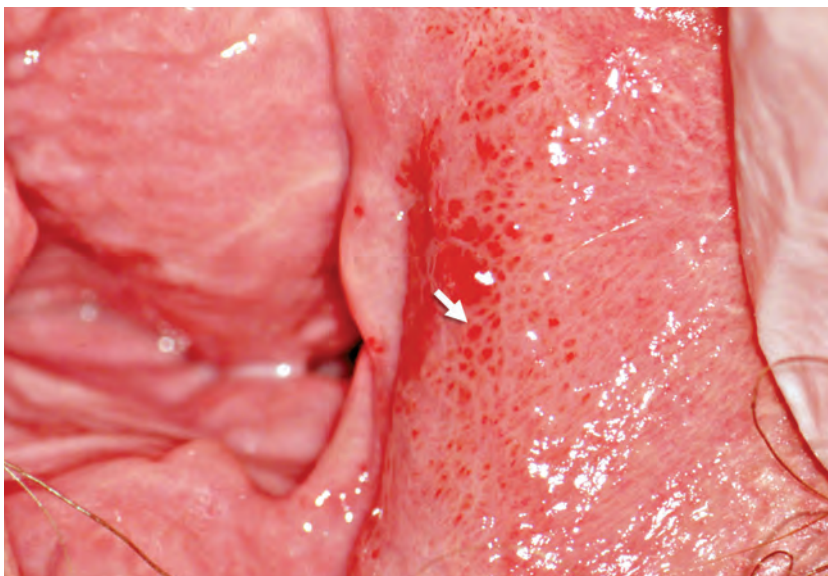


Figure 96 - Inflammatory patched capillaries (arrow) involve the medial aspect of the left labium minor.



Figure 97 - Candida vulvitis has produced widespread patches of dilated capillaries on the mucosal surface of labia minora and on fourchette.



Figure 98 - Dystrophic cervix in menopause showing patched dilated capillaries (arrow) and vascular effusions (e).

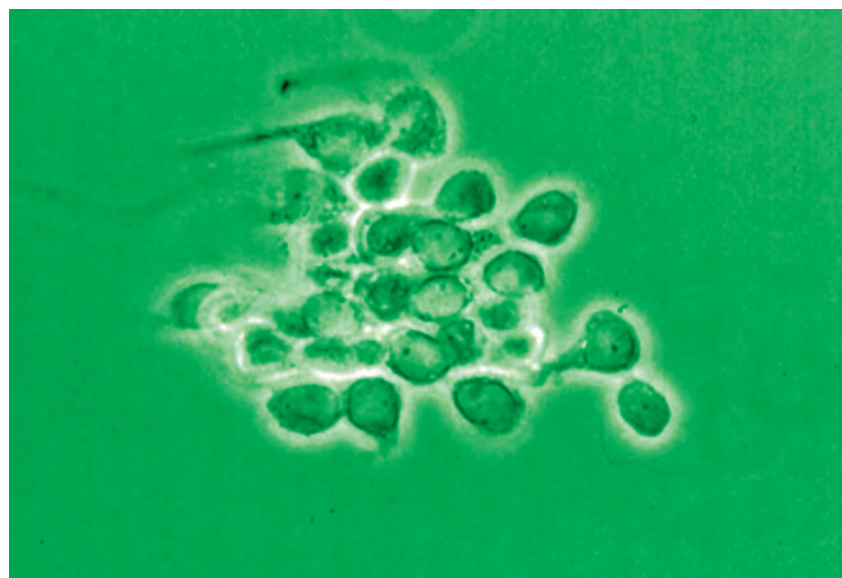


Figure 99 - This microphotograph shows an atrophic cell pattern, characterized by a cluster of basal cells.



Figure 100 - Perianal acetowhite area with coarse mosaic (arrow). Punch biopsy disclosed a high-grade anal intraepithelial neoplasia.

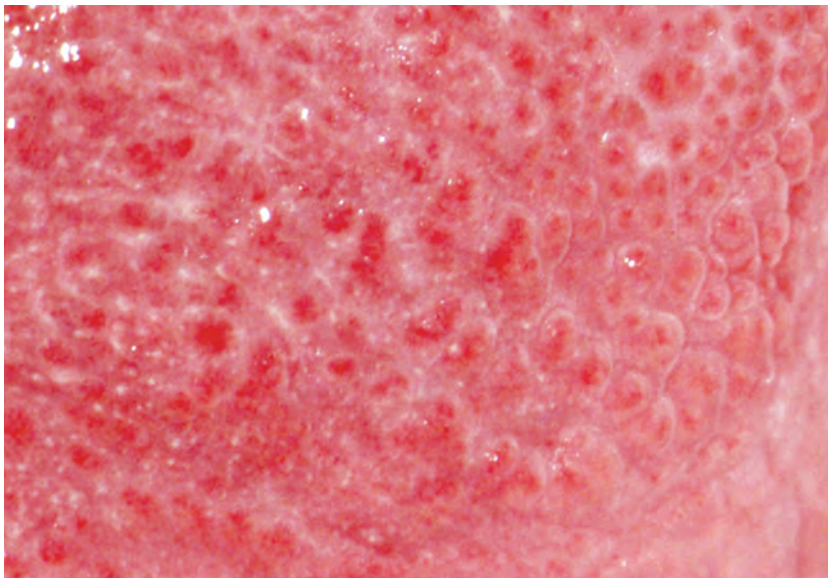


Figure 101 - Papillary punctation, characterized by a coarse punctation that rises up from the plane of the surrounding abnormal epithelium, appearing in the form of papillae. Histology showed in situ carcinoma, with early stromal invasion.

coarse punctation may rise up from the plane of the surrounding abnormal epithelium, appearing in the form of papillae (Figure 101). This colposcopic change is known as *papillary punctation*.

In the *mosaic* pattern, vessels arborize within the stromal papillary ridges, form a basket-like structure around buds of abnormal epithelium and run parallel with the surface, demarcating mosaic-like avascular fields (Figure 102). After acetic acid treatment, the epithelial buds appear as small white cobbles, surrounded by the aforementioned blood vessels, defining mosaic-like avascular fields. The cobbles may be regular in size and shape, or irregular, depending on the degree of the underlying abnormality. These two colposcopic findings, which include intermediate degrees of altered vessels, distinguish

fine mosaic from coarse mosaic (2011 IFCCPC Nomenclature).

In *fine* mosaic pattern, the blood vessels in the stroma are visible as a network of fine capillaries of uniform caliber in close proximity to one another, enclosing regular epithelial cobbles (Figure 103). Fine mosaic may still turn into a nonacetowhite mature metaplastic epithelium. In the progressing change, a fine vascular texture may be observed over a faint acetowhite epithelium or a fully mature metaplastic epithelium. This finding is referred to as *mosaic base* (Figure 104).

Coarse mosaic is characterized by a greater irregularity of the epithelial 'tiles' which appear bigger and more variable in size (Figure 105) and are often seen raised (Figure 106). The furrows between the epithelial

MOSAIC pattern

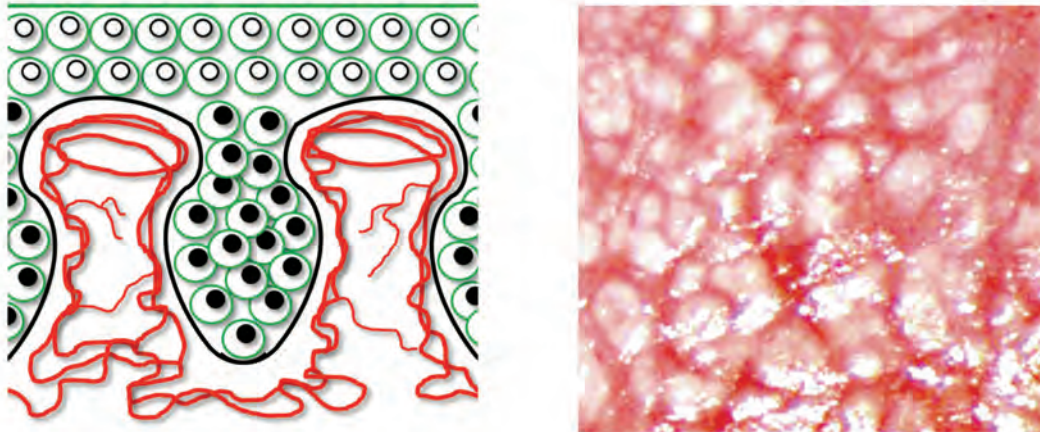


Figure 102 - Diagrammatic representation and colposcopic appearance of coarse mosaic.

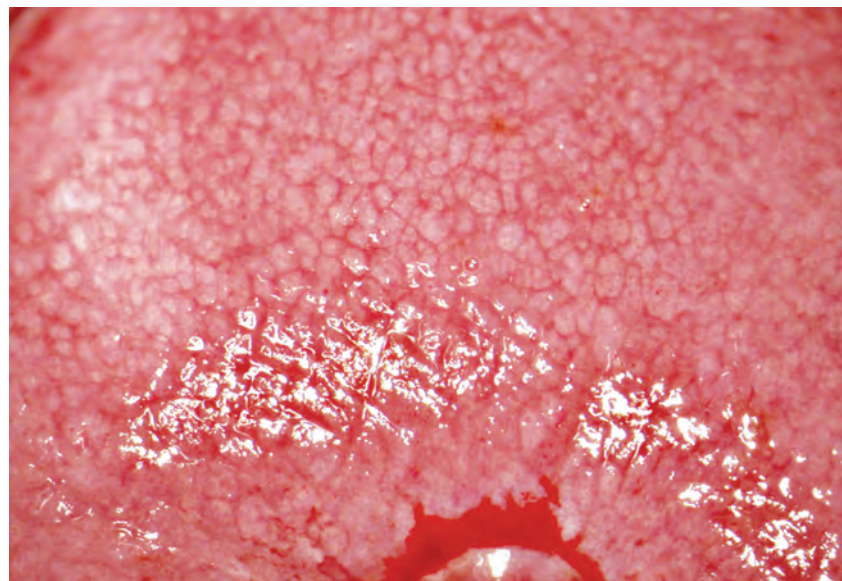


Figure 103 - Fine mosaic showing regular cobbles, surrounded by capillaries of uniform caliber.

cobbles are more widely spaced and intensely red. Intercapillary distance depends upon the severity of the lesion.

Coarse punctuation and coarse mosaic often occur in high-grade SIL and early preclinical invasive cancer. When the two vascular patterns are overlapped in the same area, the dilated capillary loop can be

seen in the center of each mosaic tile, defining the so-called *umbilication* (Figure 107).

Reverse mosaic is a rare colposcopic finding because it is short-lived and indicates the beginning of atypical metaplasia (Figure 108). It is characterized by small red islands corresponding to the tips of former columnar papillae, circumscribed by white

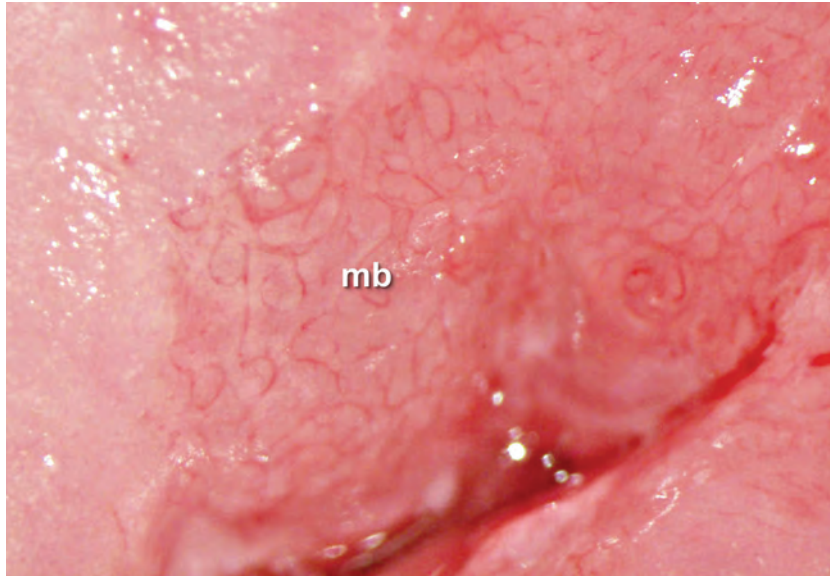


Figure 104 - The fine vascular texture over a mature metaplastic epithelium characterizes the mosaic base (mb).

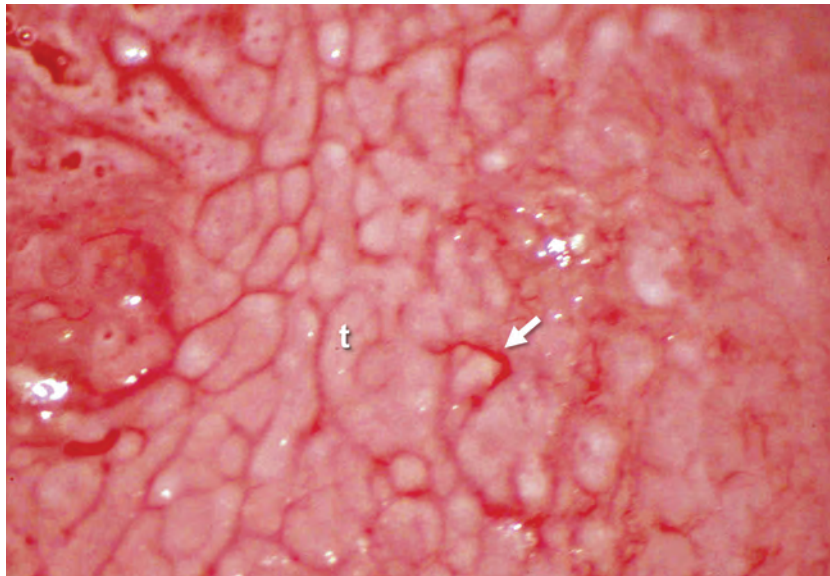


Figure 105 - Coarse mosaic with irregular tiles (t) and capillaries of different caliber (arrow).

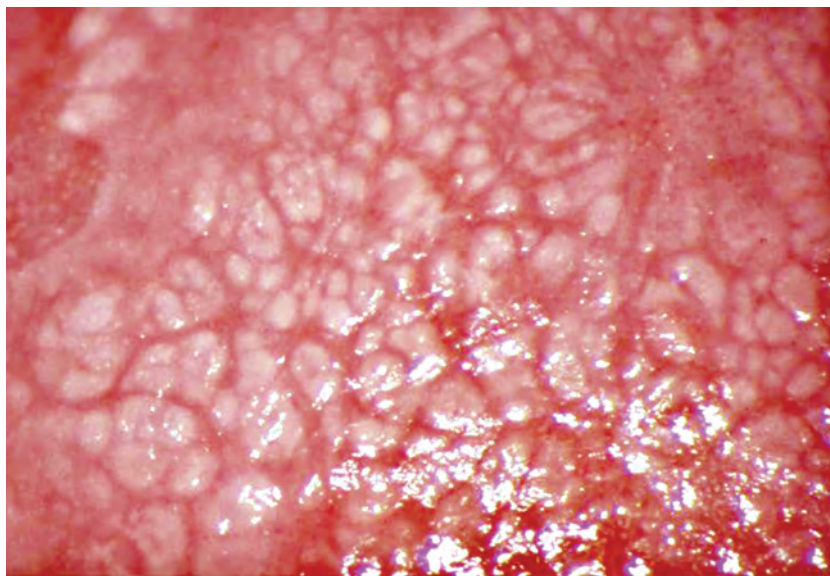


Figure 106 - The tiles of this coarse mosaic appear variable in size and raised. Histology showed CIN 3.

Figure 107 - Coarse mosaic and punctation vascular pattern are overlapped (arrow). This colposcopic appearance is named umbilication. This lesion was shown to be composed of HPV/CIN 3.

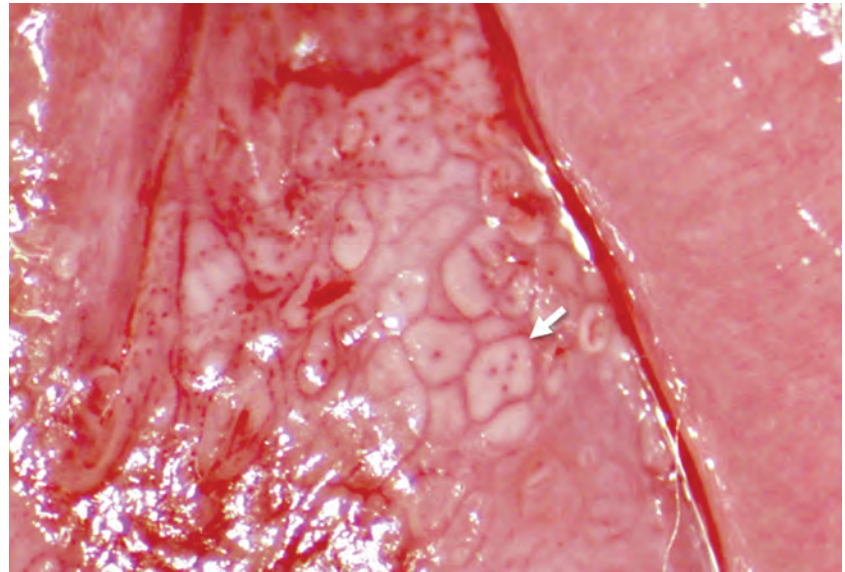


Figure 108 - Reverse mosaic characterized by raised small red areas (r), circumscribed by acetowhite metaplastic epithelium (arrow). This colposcopic appearance is associated with punctation (p) and mosaic vascular pattern (m).

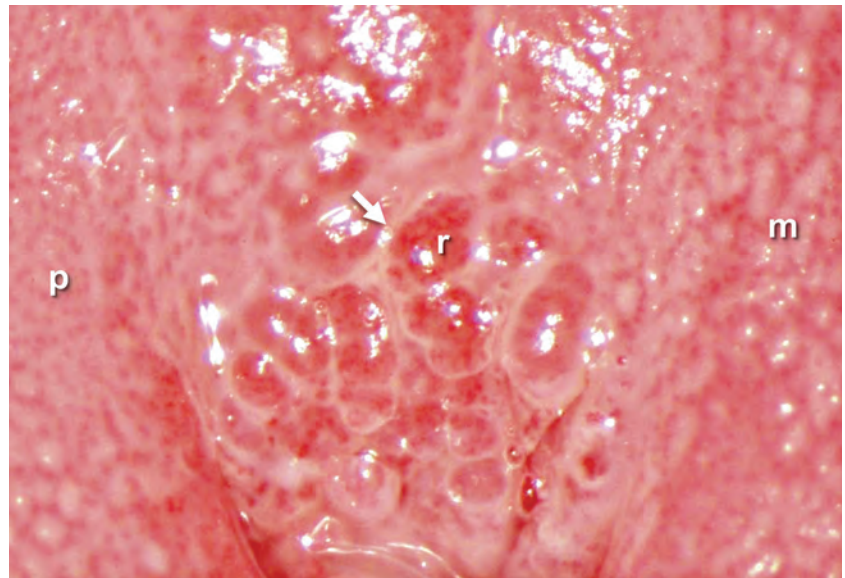
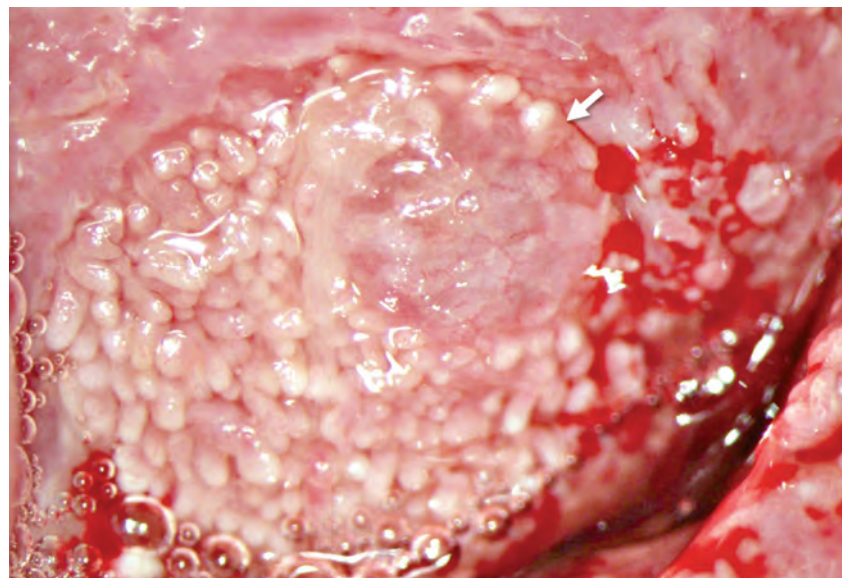


Figure 109 - Despite the absence of any atypical vessels, the smooth raised area (arrow) over acetowhite papillae proved to be adenocarcinoma in situ.



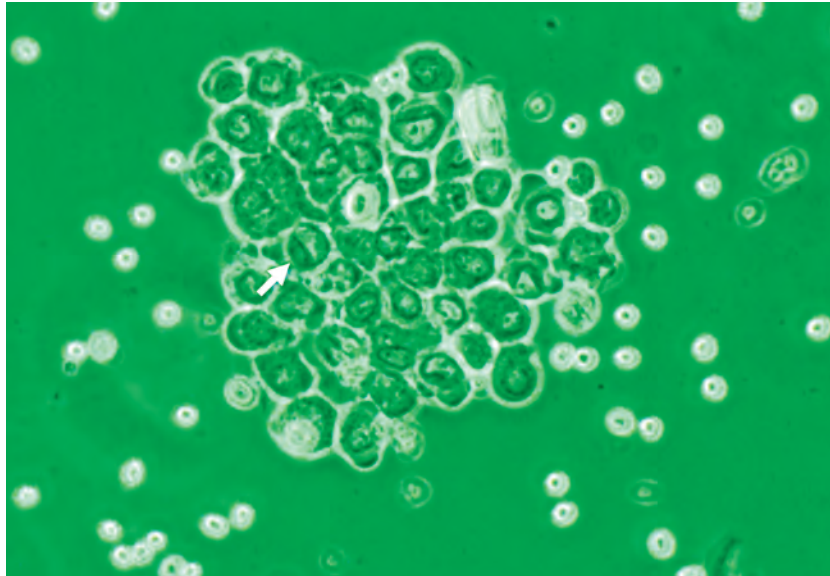


Figure 110 - Wet mount appearance showing a cluster of neoplastic cells in adenocarcinoma in situ. The nuclei appear different in size (anisokaryosis) and characteristically eccentric (arrow).

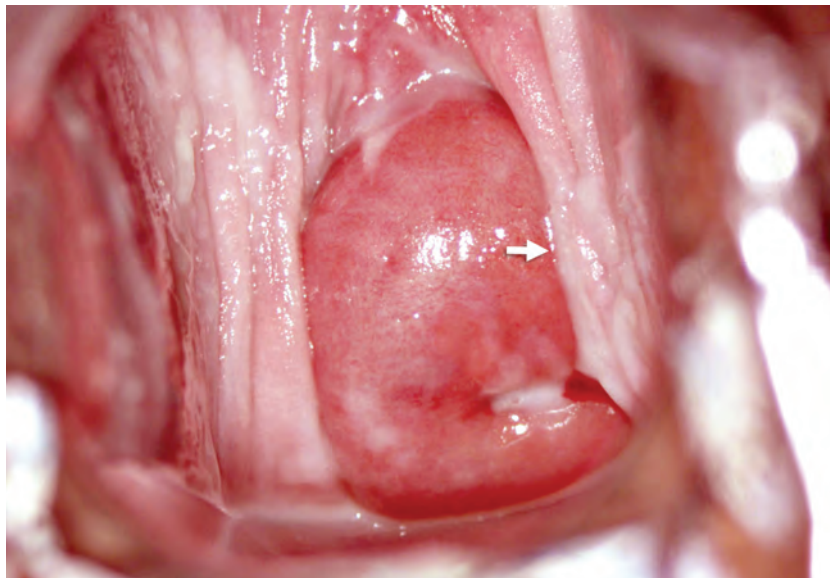


Figure 111 - The presence of congenital fibrous brindles (arrow) can limit the complete inspection of the cervix.



Figure 112 - The vaginal vault, following hysterectomy, shows lateral recesses (arrows) known as "dog ears".

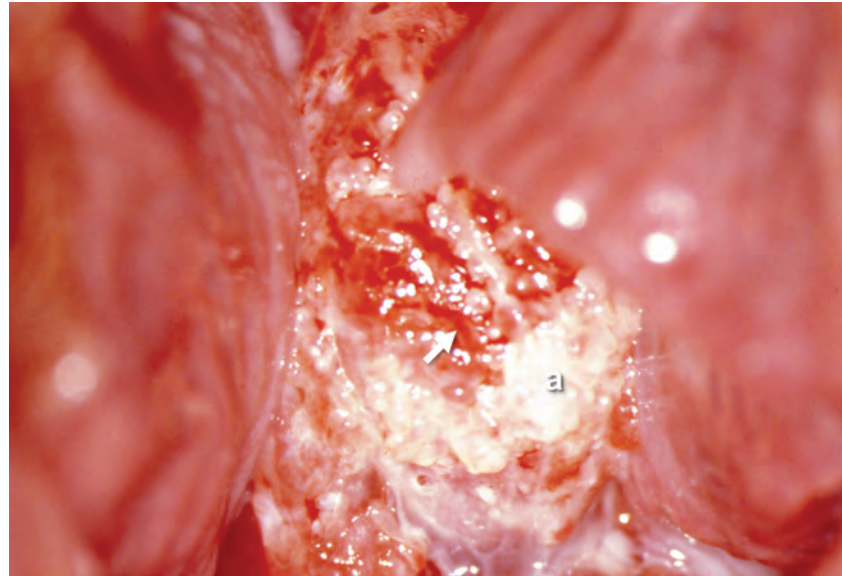


Figure 113 - The lateral vaginal recess, following hysterectomy, harbors an exophytic tissue with uneven surface, dense acetowhite area (a) and dilated atypical vessels (arrow). Excision biopsy and resultant pathology demonstrated squamous carcinoma.

metaplastic squamous epithelium. When atypical epithelium progresses, reverse mosaic soon turns into either punctuation or mosaic.

Fine punctuation is often combined with equally fine mosaic and coarse punctuation may coexist with coarse mosaic in the same lesion. This finding is not surprising because both punctuation and mosaic patterns develop in a similar atypical direction within the transformation zone. Even if vascular alterations represent the first morphologic feature in the development of cervical neoplasia, it is useful to point out that punctuation and mosaic may also be found in normal epithelium and outside the transformation zone but the same vascular patterns within the TZ are more likely to represent epithelial atypia.

On the other hand, many squamous intraepithelial

lesions and glandular atypia do not have colposcopically atypical vessels (Figures 109, 110).

It is worth noting that no single colposcopic finding is pathognomonic of any one lesion.

There exist particular anatomical conditions that limit the colposcopic inspection. In fact, some congenital vaginal stenosis due to fibrous bridles (Figure 111) limit the complete detection of the cervix or surgical outcomes following total hysterectomy, may hinder a complete investigation of the vaginal vault. In this case, the vaginal vault is frequently distorted with mucosal recesses at the 3 and 9 o'clock positions (Figure 112). These lateral indentations usually termed as “dog ears” must be inspected with Desjardin’s or Kogan’s forceps, and carefully scraped when PAP smear is carried out, because can harbor neoplasia (Figure 113).