Oral Precancerous lesions & conditions

DEPARTMENT OF ORAL AND MAXILLOFACIAL PATHOLOGY & ORAL MICROBIOLOGY

Premalignant lesions/conditions

- Forerunner of cancer
- Encompass a histological continuum between the normal mucosa at one end and the high-grade dysplasia/carcinoma in situ, at other, establishing a model of neoplastic progression.
- Distinguished from malignancy
  - by lack invasiveness
  - lack of metastasis
- High potential to undergo malignant transformation

Definitions (WHO- 1978)

Precancerous lesions:

"A morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart "

- There is alteration of the clinical appearance of the affected epithelial tissue.

Precancerous conditions:

"A generalized state associated with a significantly increased risk of cancer"

- It does not necessarily alter the clinical appearance of local tissue, but is associated with a greater than normal risk of development of cancer in affected tissue.

Potentially Malignant Disorders

- The terminology precancerous lesion implies that the lesion will follow an irreversible and inevitable progression to OSCC.
- But not all precancerous lesions progress to cancer , nor all cancers necessarily originate from such lesions hence the term Potentially Malignant Disorder is more appropriate.
- Identification of such lesions through clinical, histological and more recently through molecular level changes, helps early detection and treatment of Ca.

Dysplasia

- ***It comprises a loss in the uniformity of the individual cell as well as a loss in their orientation.***
- **DYSPLASIA – ABNORMAL GROWTH**
- Principally in epithelium
- It's a reversible & controlled cellular alterations
- Characteristically associated with protracted chronic irritation or inflammation
- When stimulus removed : revert to normal

Dysplasia

Cellular adaptation

Hyperplasia followed by atrophy

Reversible changes

Dysplasia

Irreversible changes

Cell death or neoplastic transformation

Cellular Atypia :

In the course of premalignancy to cancer, visible physical changes are taking place at the cellular level, these changes are called cellular atypia.

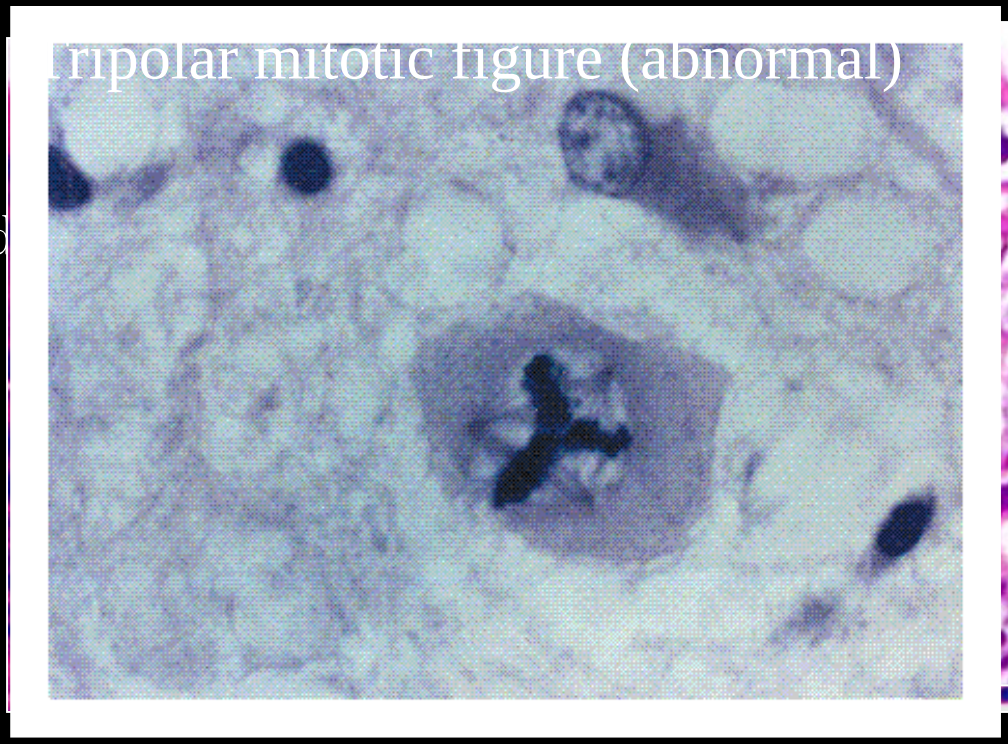
Dysplasia :

Dysplasia is seen at tissue level. It is encountered principally in the epithelia. It comprises a loss in the uniformity of the individual cells, as well as a loss in their architectural orientation.

Dysplastic changes

Cellular changes:

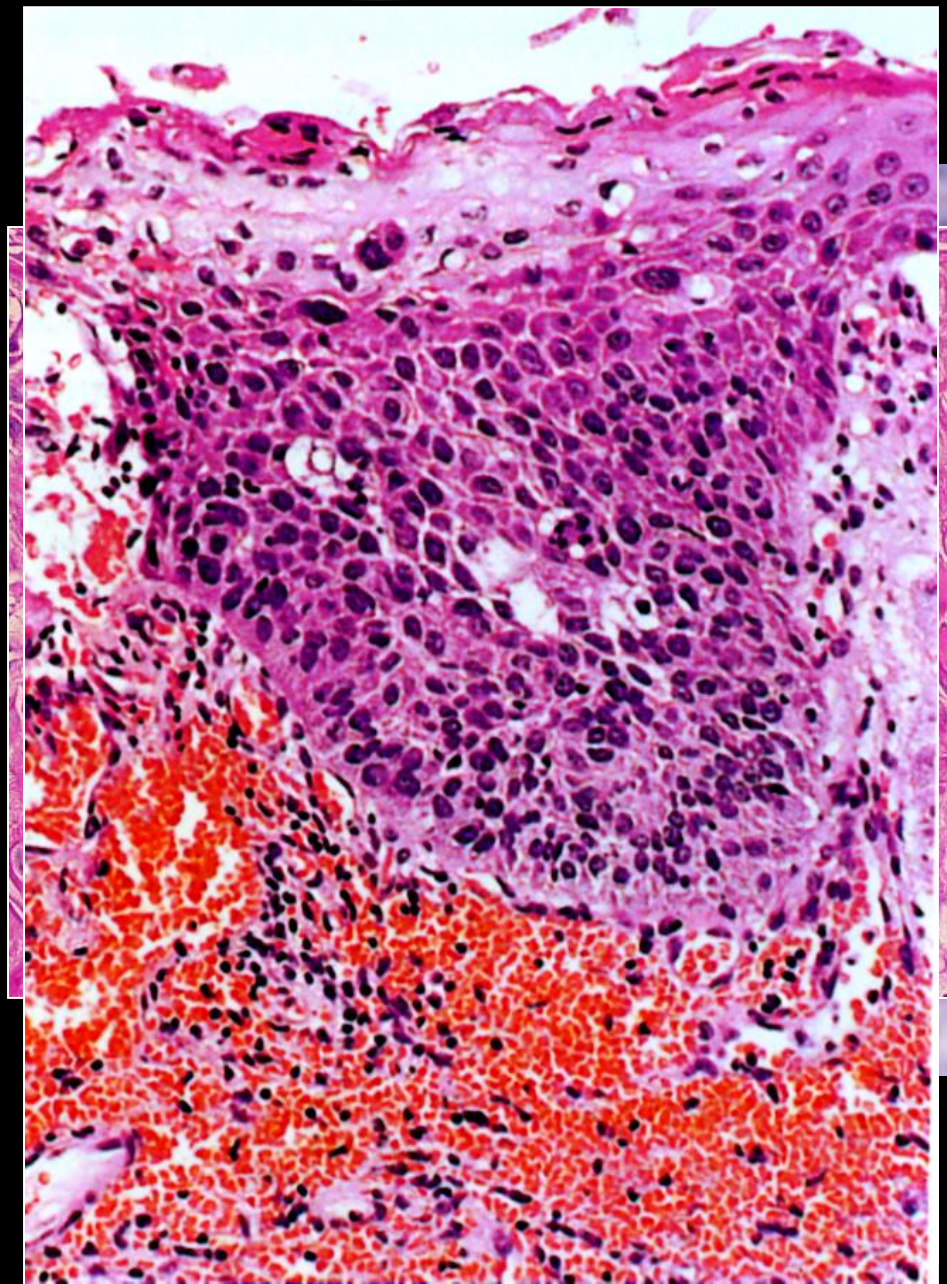
- **Pleomorphism** : Variation in size & shape of cell
- **Anisonucleosis** : variation in nuclear size
- **Hyperchromatism** : deeply stained nuclei
- **Large and prominent nucleoli**
- **Increased Nuclear - cytoplasmic ratio** – from 1:4 to 1:1 at expense of cytoplasmic volume
- **Abnormal mitotic figures** : bipolar , tripolar
- **Increased Mitotic figures** : abundant
- **Individual cell keratinization**

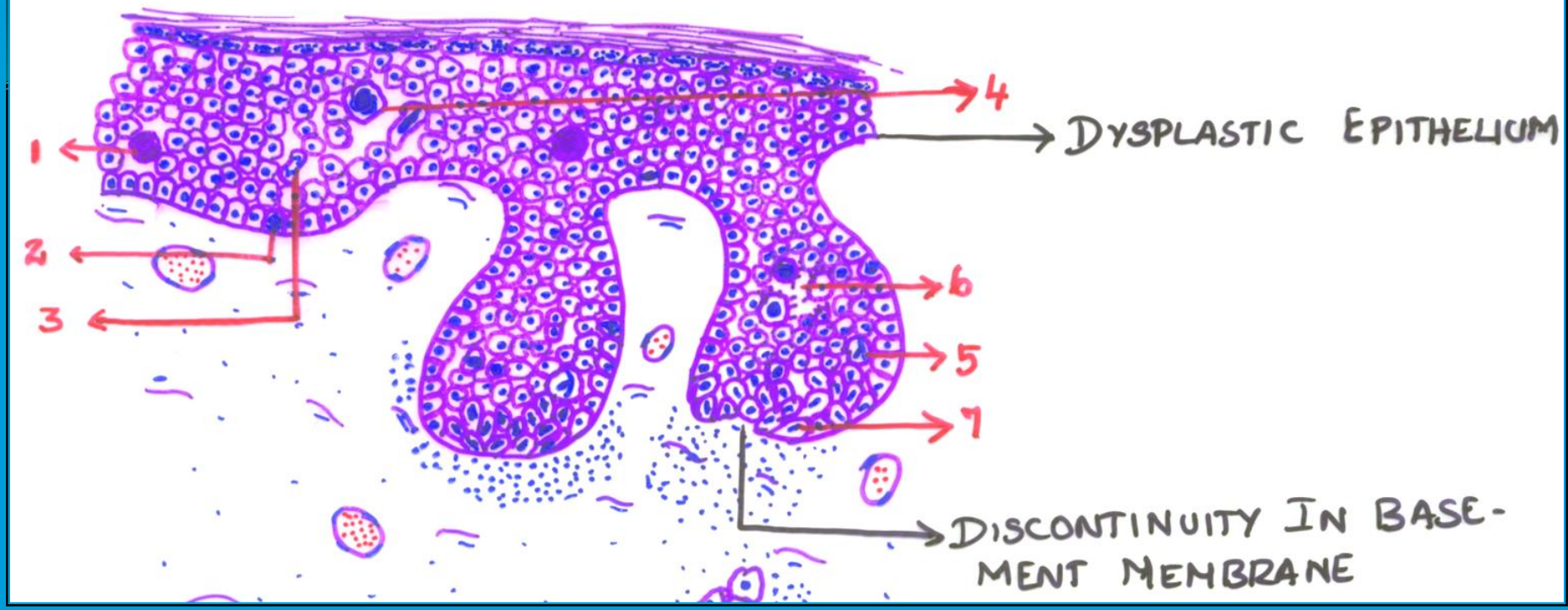


Dysplastic changes

Tissue changes :

- Loss of polarity
- Basal cell hyperplasia
- Bulbous drop shaped rete pegs
- Abnormal stratification of epithelium
- Dyskeratosis : premature karatinization
- Reduction in cellular cohesiveness

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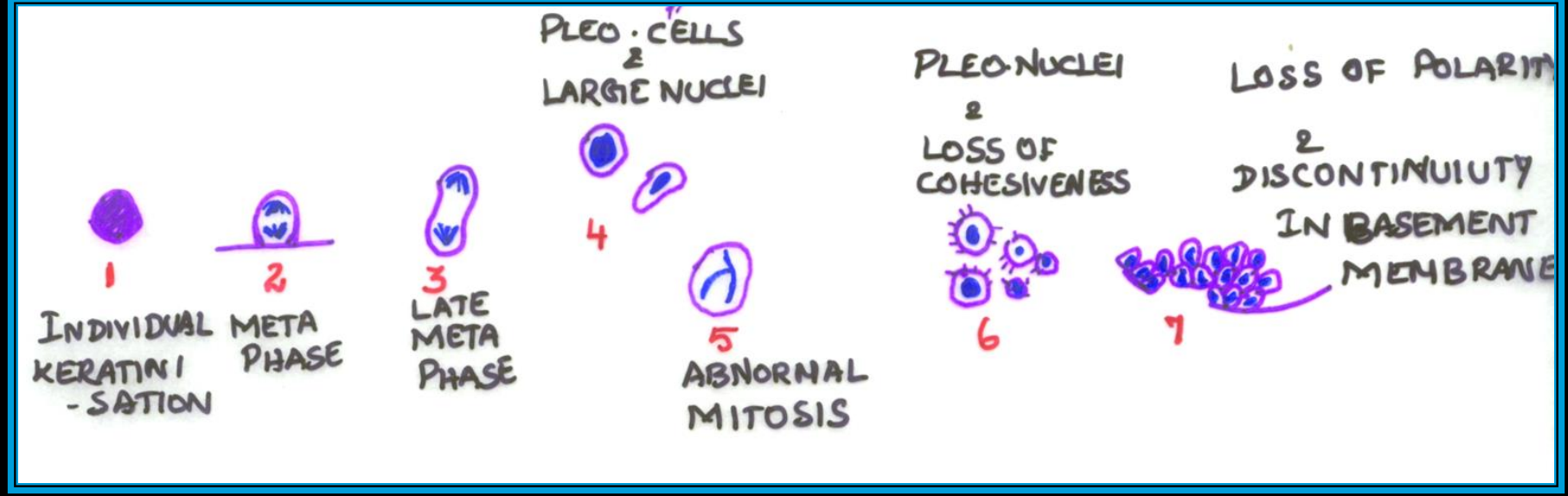
DYSPLASTIC EPITHELIUM
6
5
7
DISCONTINUITY IN BASE-
MENT MEMBRANE


1
INDIVIDUAL KERATINI -SATION
2
META PHASE
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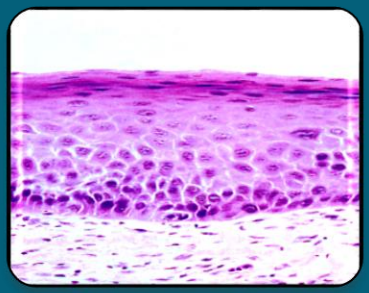
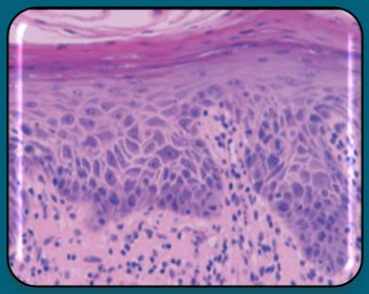
LATE META PHASE
PLEO. CELLS & LARGE NUCLEI
4
5
ABNORNAL MITOSIS
PLEO-NUCLEI & LOSS OF COHESIVENESS
6
LOSS OF POLARITY & DISCONTINUITY IN BASEMENT MEMBRANE
7

Types : Three types



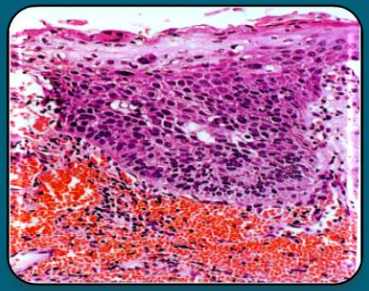
Mild dysplasia :

Alterations limited to basal & parabasal layers



Moderate dysplasia :

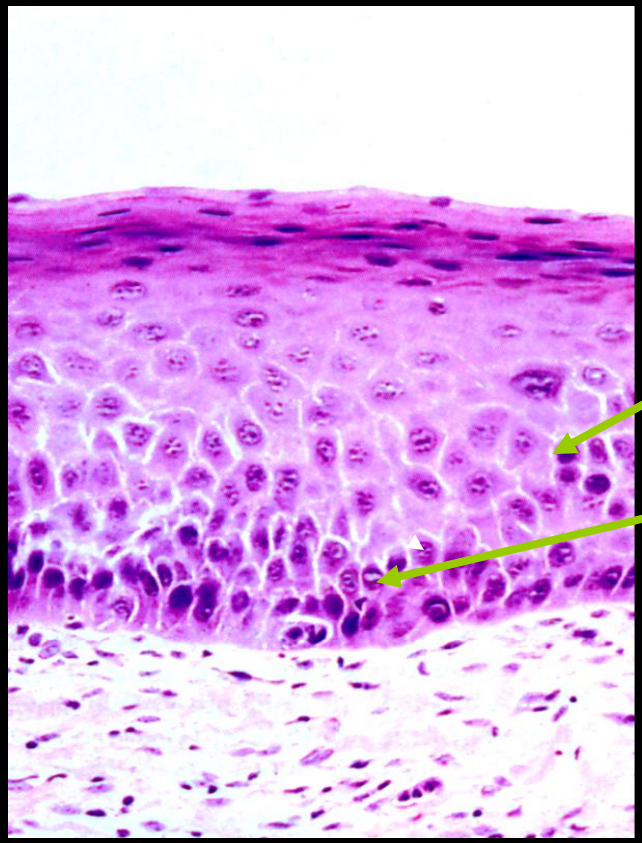
Involve basal layer to mid portion of spinous layer

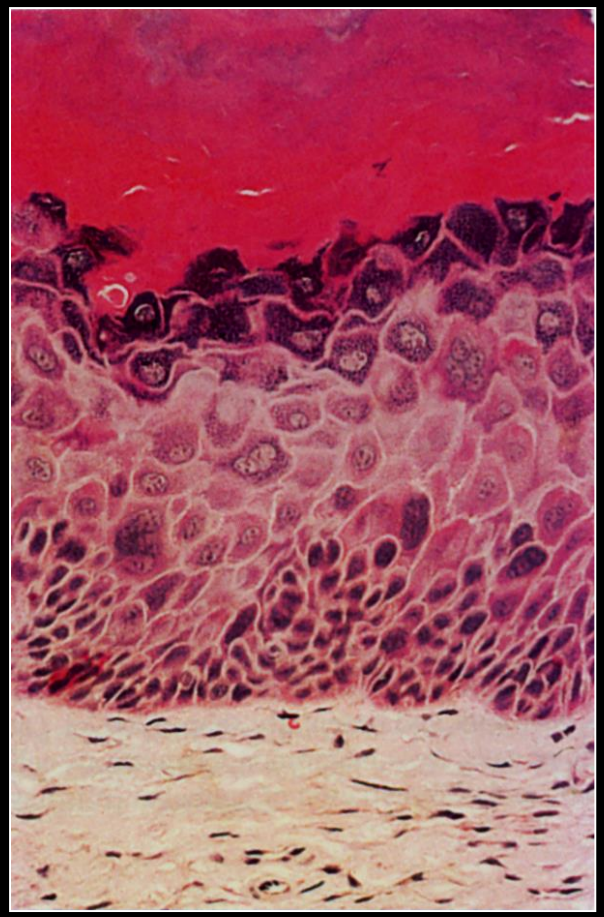


Severe dysplasia :

More than 2/3 involved . Only superficial cells normal

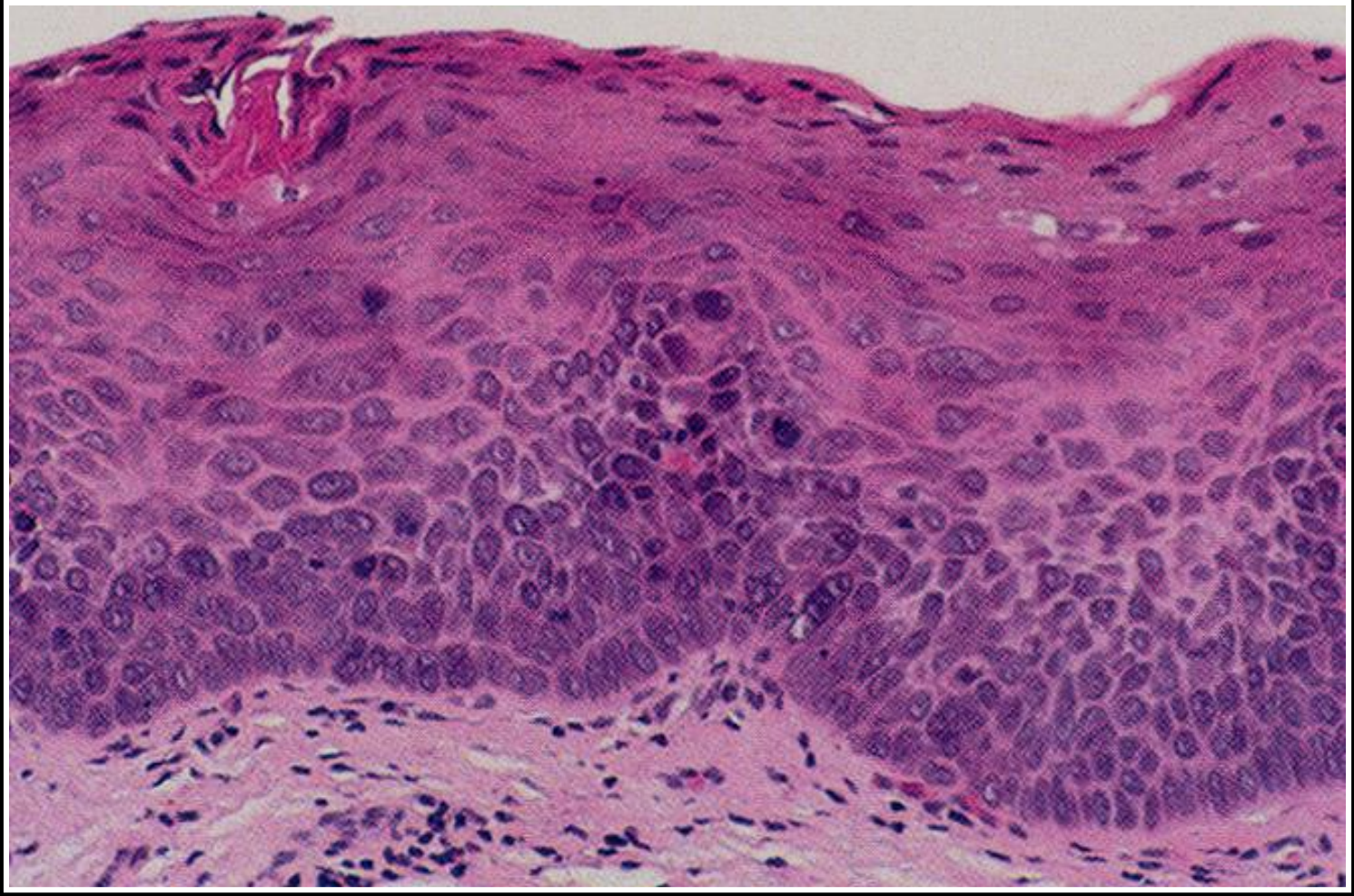
Mild dysplasia





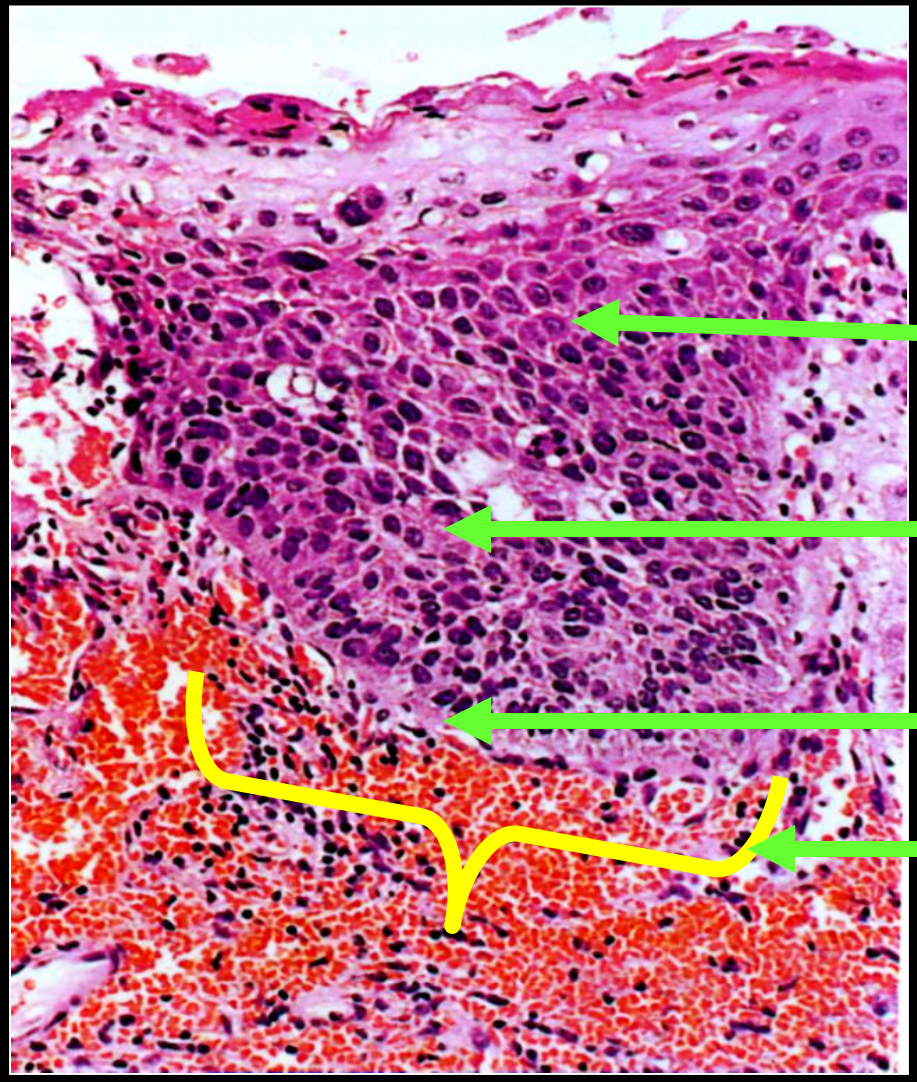
Alterations limited to basal & parabasal layers

Moderate dysplasia



Involve basal layer to midportion of spinous layers

Severe dysplasia



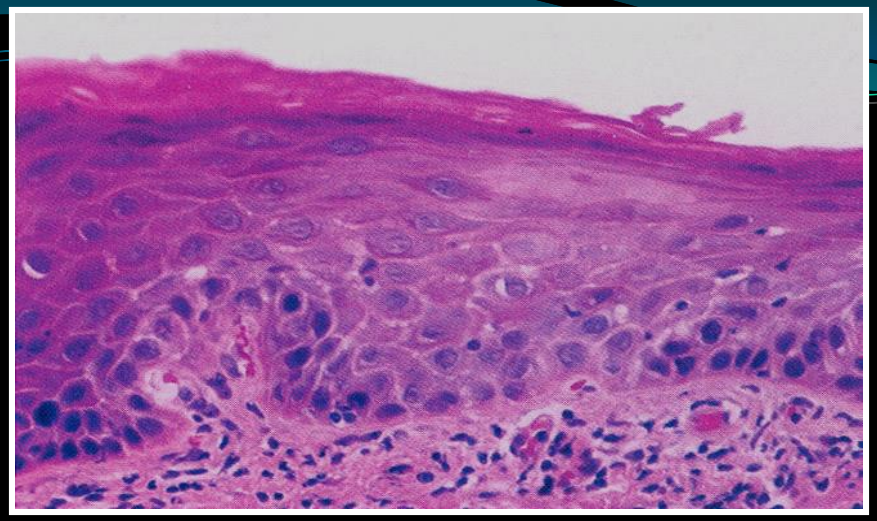
Hyperchromatism

irregular stratification

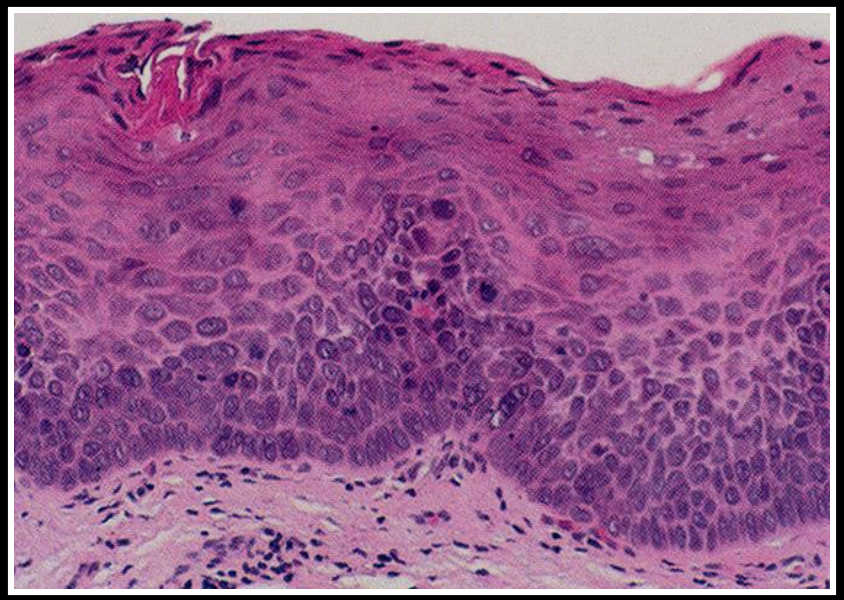
loss of polarity

bulbous rete peg

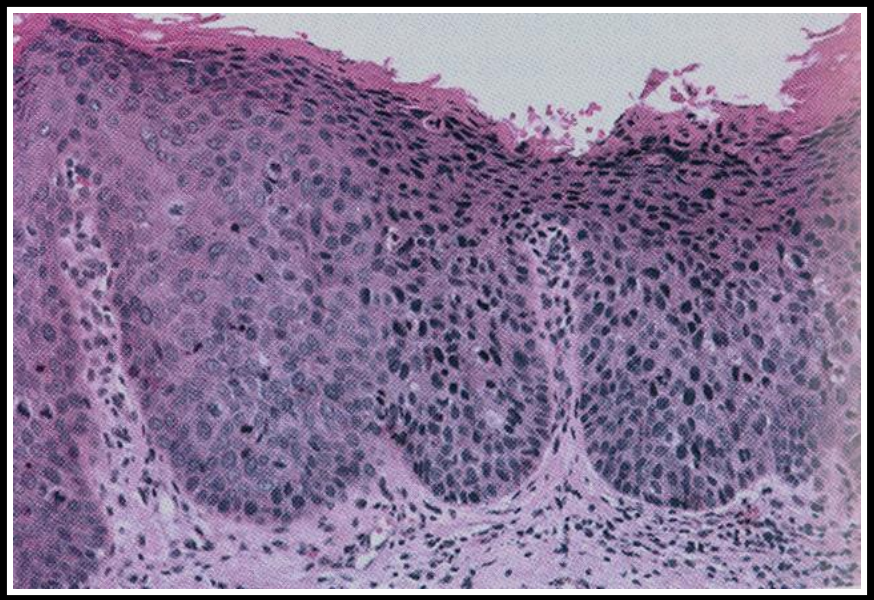
Only superficial cells well differentiated



Mild

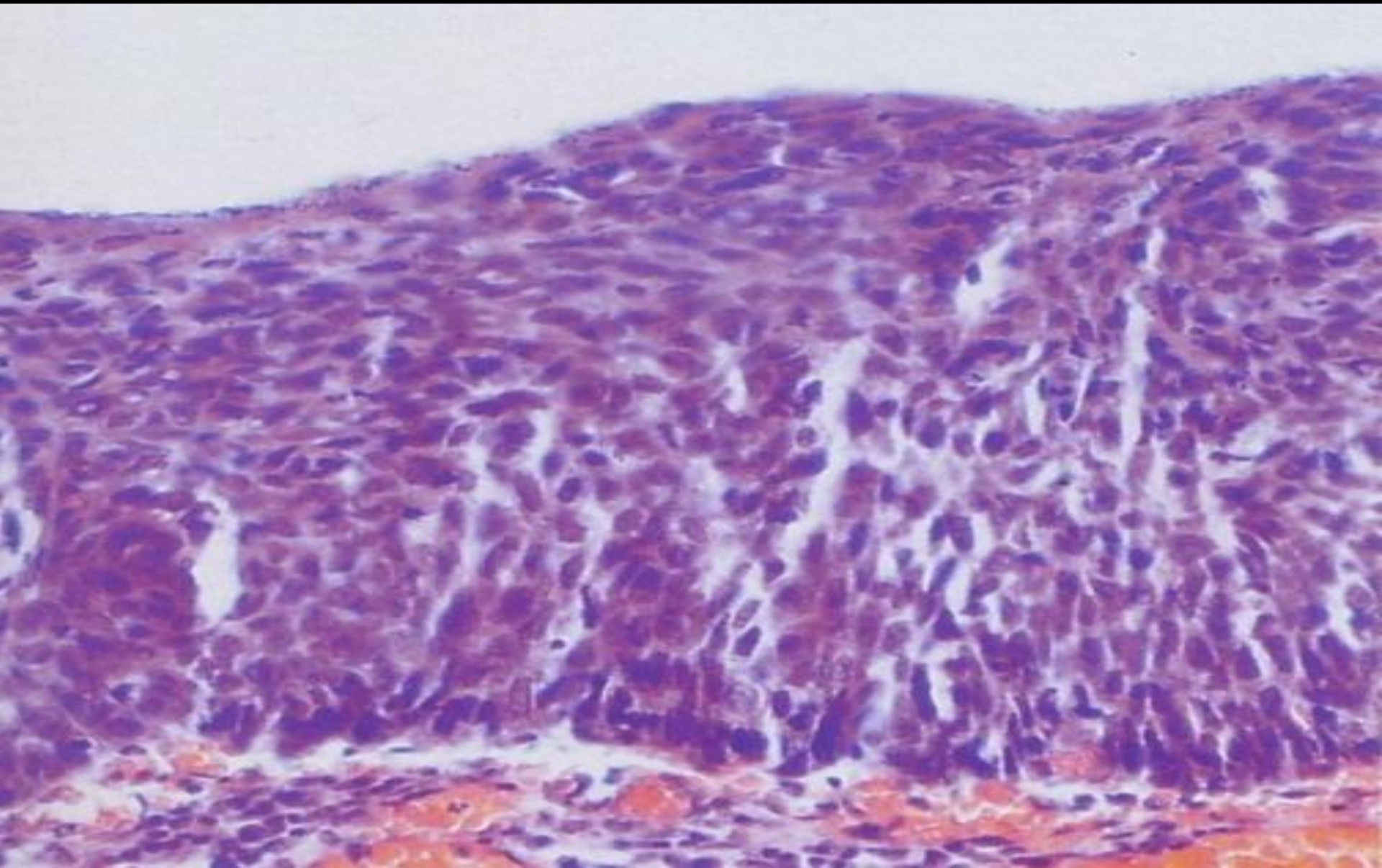


Moderate



Severe

Ca in situ (Intraepithelial carcinoma)



The more dysplastic the lesion is, higher the chance of malignant transformation of the lesion into a carcinoma

Precancerous lesions & conditions

Precancerous lesions

- Leukoplakia
- Erythroplakia
- Intraepithelial carcinoma
  (Ca in situ)
- Palatal keratosis ass. with reverse smoking

Precancerous conditions

- Submucous fibrosis
- Lichen planus
- Actinic Cheilosis
- Sideropenic dysphagia
- Syphilis
- Discoid Lupus erythematosus

LEUKOPLAKIA (Leukokeratosis)

Leukoplakia is simply defined as a **white patch on the mucosa which will not rub or scrap off.**

WHO defined Leukoplakia as a **white plaque or patch which cannot be classified clinically & histologically as any other disease and is not associated with any other physical or chemical agent, except the use of tobacco.**

- **Greek words : Leucos – white , Plakia - patch**
- Localised hyperkeratosis – white appearance – due to wetting of keratotic patch with saliva
- Most common potentially malignant lesion of oral mucosa – premalignant lesion
- an adaptive response against some forms of sustained low grade irritants
- Definitive diagnosis : histopathologically

- **Diagnosis depends on exclusion of other entities which appear as oral white lesions like L.P., OSMF, cheek biting, leukoedema etc.**
- **It is a clinical descriptive term, not a histological diagnosis**

Etiology

- **Tobacco** : smoking 80%

  Important sources of irritation of mucous membrane are not only the combustion products brought about by the burning tobacco and the heat, but also the materials which leach out of the tobacco when it is chewed or, in the case of snuff, allowed to rest against moist mucosa which are carcinogenic.

- **Alcohol :** mouth rinses with alcohol more than 25%

  It may be irritating to the mucosa. Its effect may be synergistic to other etiological factors.

- **UV radiations:** lower lip , chronic & excessive exposure UV light from sunlight

- **Trauma** : chronic mechanical irritation , frictional keratosis , reversible

- **Candida Albicans :**

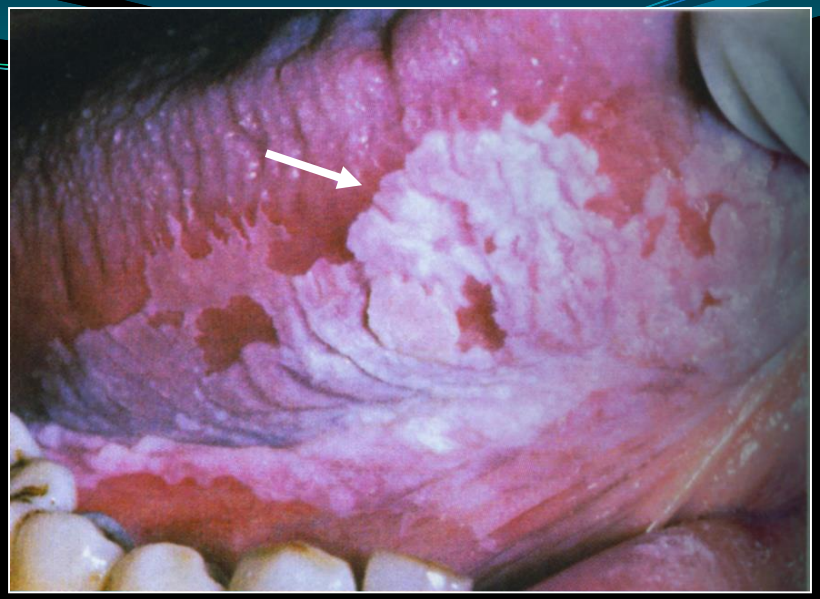
Candida albicans has been frequently reported occurring in association with leukoplakia. It is not known whether the organisms are responsible for the initiation of the lesion or whether they are only secondary invaders.

Epithelial dysplasia occurs four to five times more frequently in Candida Leukoplakia than in Leukoplakia in general.

Candida albicans has a catalytic effect in the transformation of carcinogenic nitrosamine from its precursors.

Mis : Nutritional deficiency, xerostomia, idiopathic

Clinical features



- Age – over 40 Yrs
- Prevalence : 1.5% – 4.3%
- Site: lip vermilion , buccal mucosa , gingiva. floor of mouth , tongue
- C/F varies & change with time
- Early or mild lesions : soft, translucent
- Thin leukoplakia : elevated plaque , reversible
- Thick , white appearance , fissures may developed : Thick or homogenous leukoplakia
- more surface irregularities : Granular or Nodular leukoplakia
- papillary projections : Varrucous leukoplakia

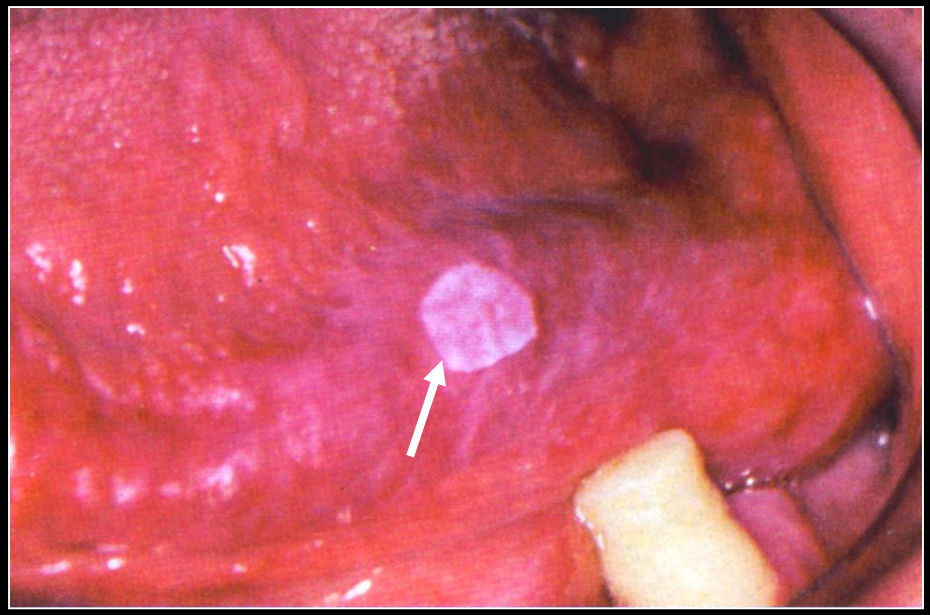
Classification of leukoplakia

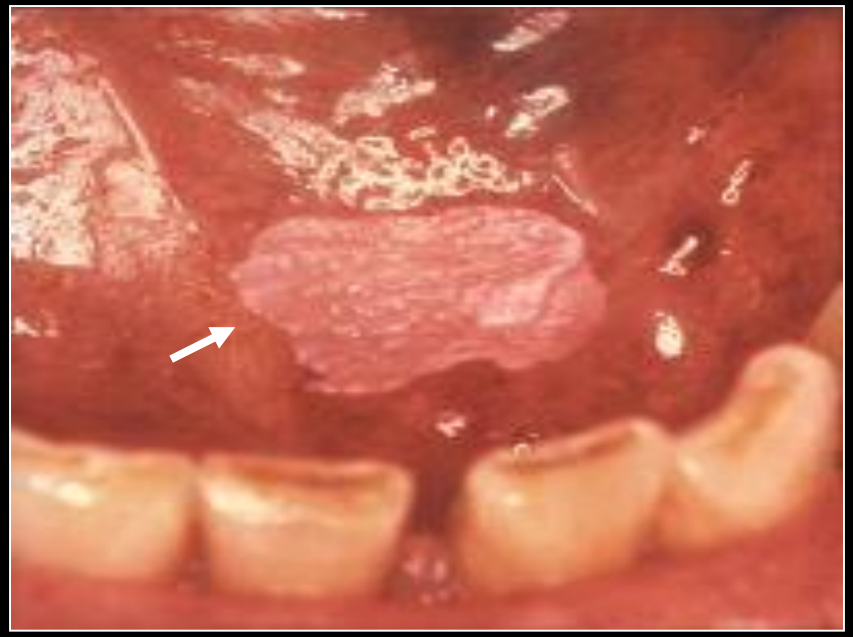
(Axell & Pindborg et al 1983)

- *Based on CLINICAL TYPE:*
  - *Homogenous*
  - *Non homogenous*
- *Based on ETIOLOGY:*
  - *Tobacco associated*
  - *Idiopathic*
- *Based on EXTENT:*
  - *Localized*
  - *Diffuse*
- *Based on risk of MALIGNANT TRANSFORMATION*
  - *High risk sites*
    - *Floor of mouth*
    - *Lateral/ventral surface of tongue*
    - *Soft palate*
  - *Low risk sites*
    - *Dorsum of tongue*
    - *Hard palate*
- *Based on HISTOLOGY:*
  - *Dysplastic*
  - *Non dysplastic*

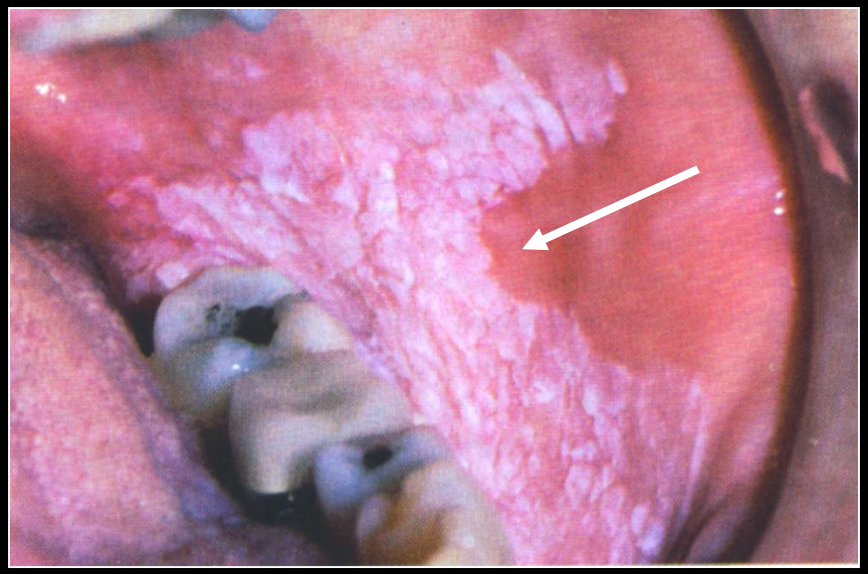
Homogenous Leukoplakia	Non-homogenous Leukoplakia
▪Completely whitish lesion ▪Smooth surface ▪Corrugated-Ebbing tide ▪Pumice like with a pattern of fine lines ▪Wrinkled- Dry,cracked surface	▪Nodular or Speckled ▪Verrucous-Slow growing ▪Ulcerated ▪Lesion is partly white and partly reddish

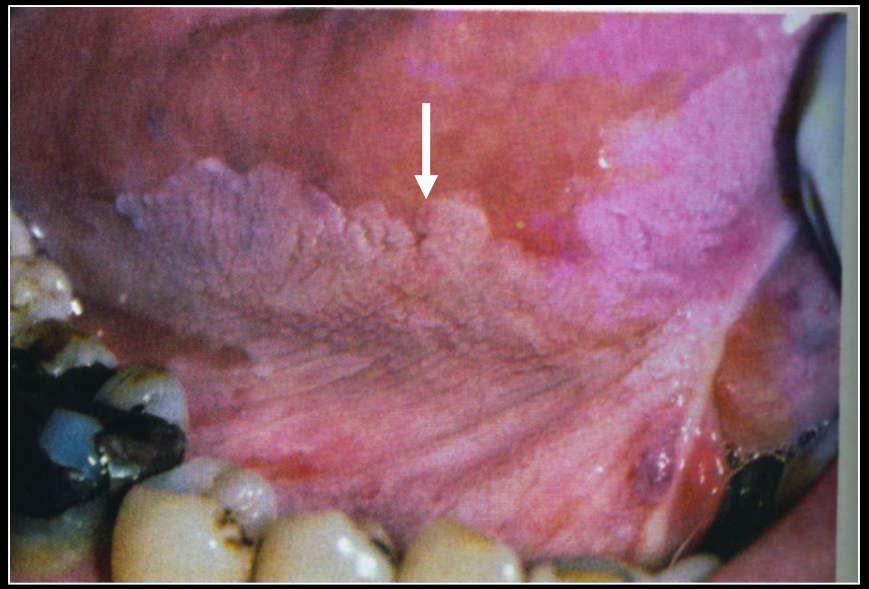
Early or mild lesions : slightly elevated plaque – soft, translucent ,sharp borders – **Thin leukoplakia**



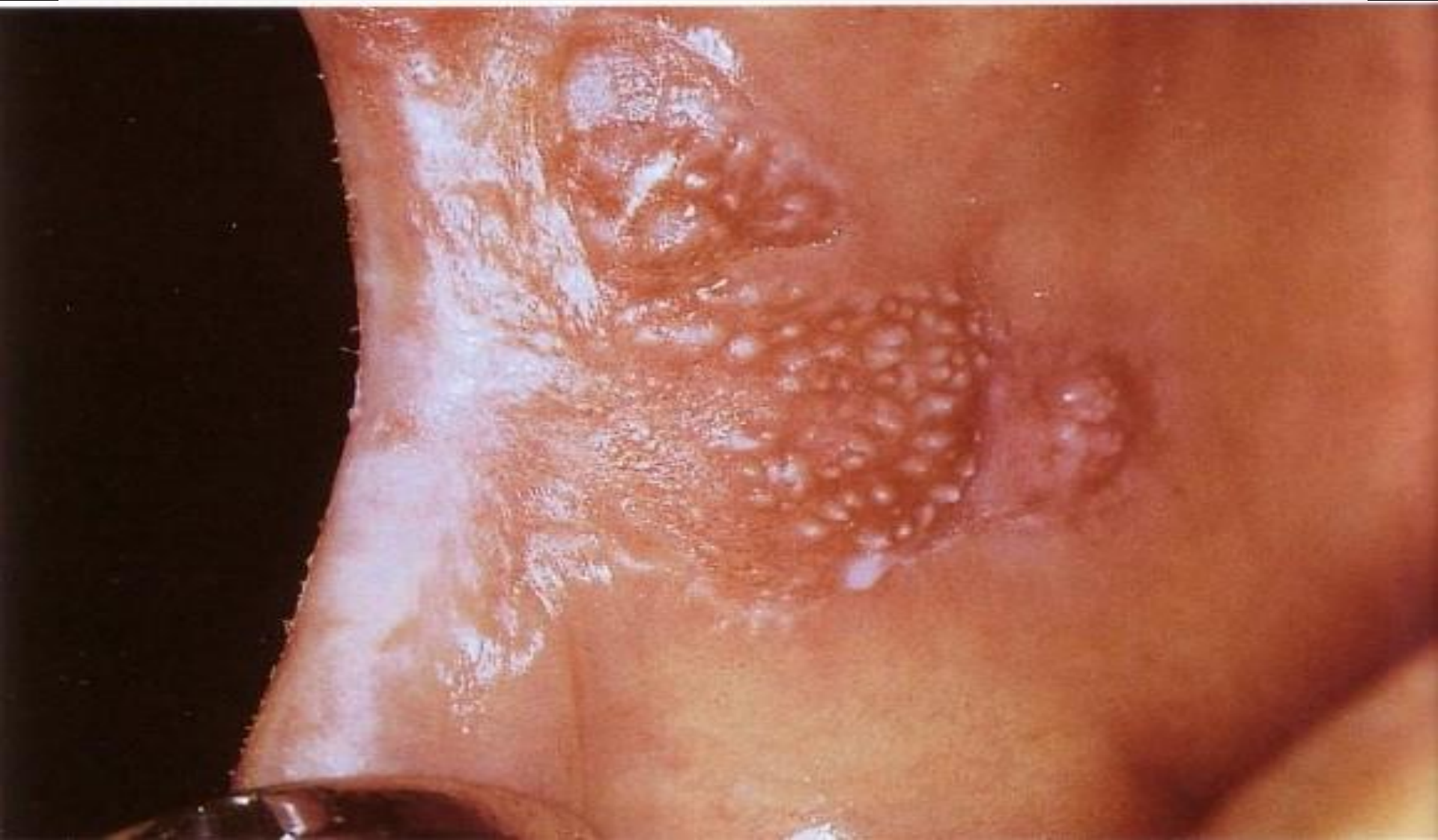


Thick , white appearance , fissures may developed – **thick homogenous leukoplakia**





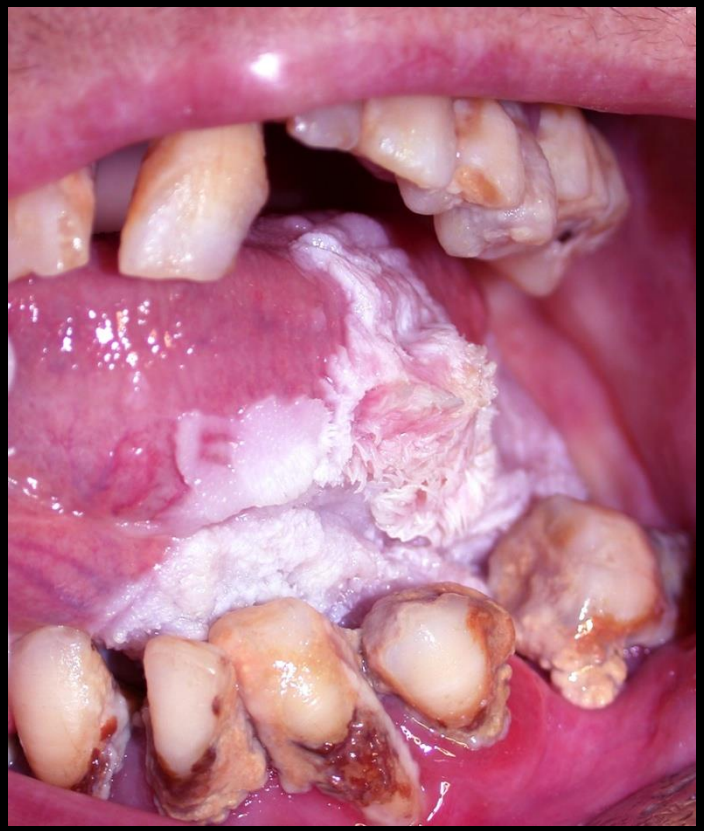
More surface irregularities (Granular or nodular leukoplakia)

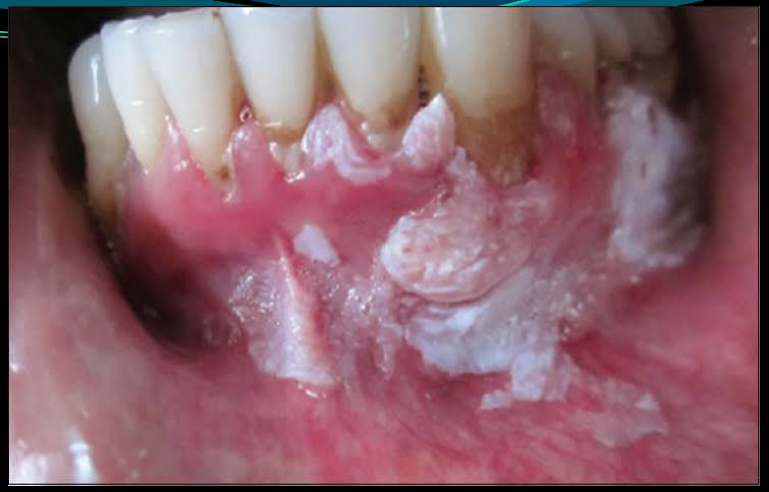


Proliferative Verrucous Leukoplakia

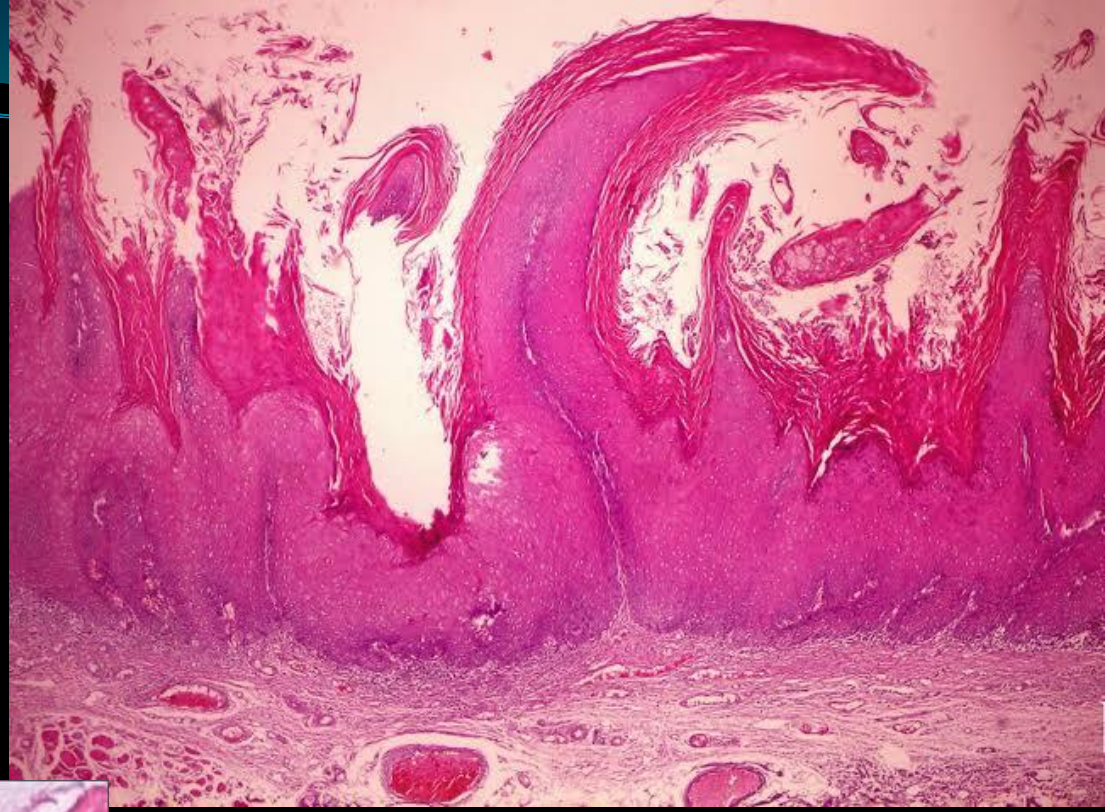
- Uncommon variant of leukoplakia
- Characterised by aggressive behavior
- Multiple keratotic plaques (multifocal) with roughened surface projections
- Evolution from a thin, flat white patch to leathery, then papillary to verrucous
- Strong female predilection
- Minimal association with tobacco use
- Strong potential for malignant transformation
  Development of squamous cell CA in over 70% of cases

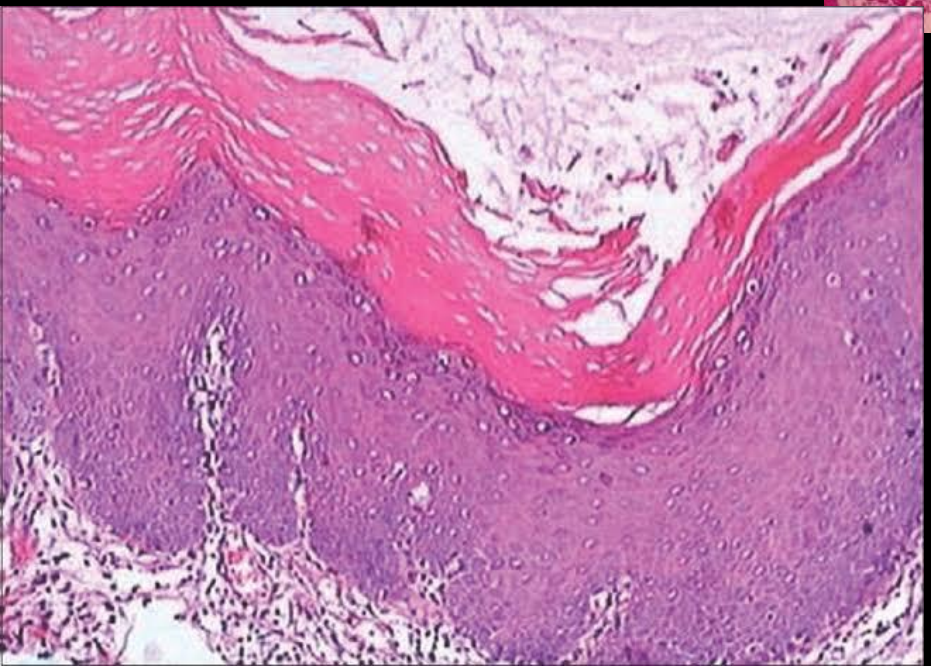
Clinical appearance of PVL



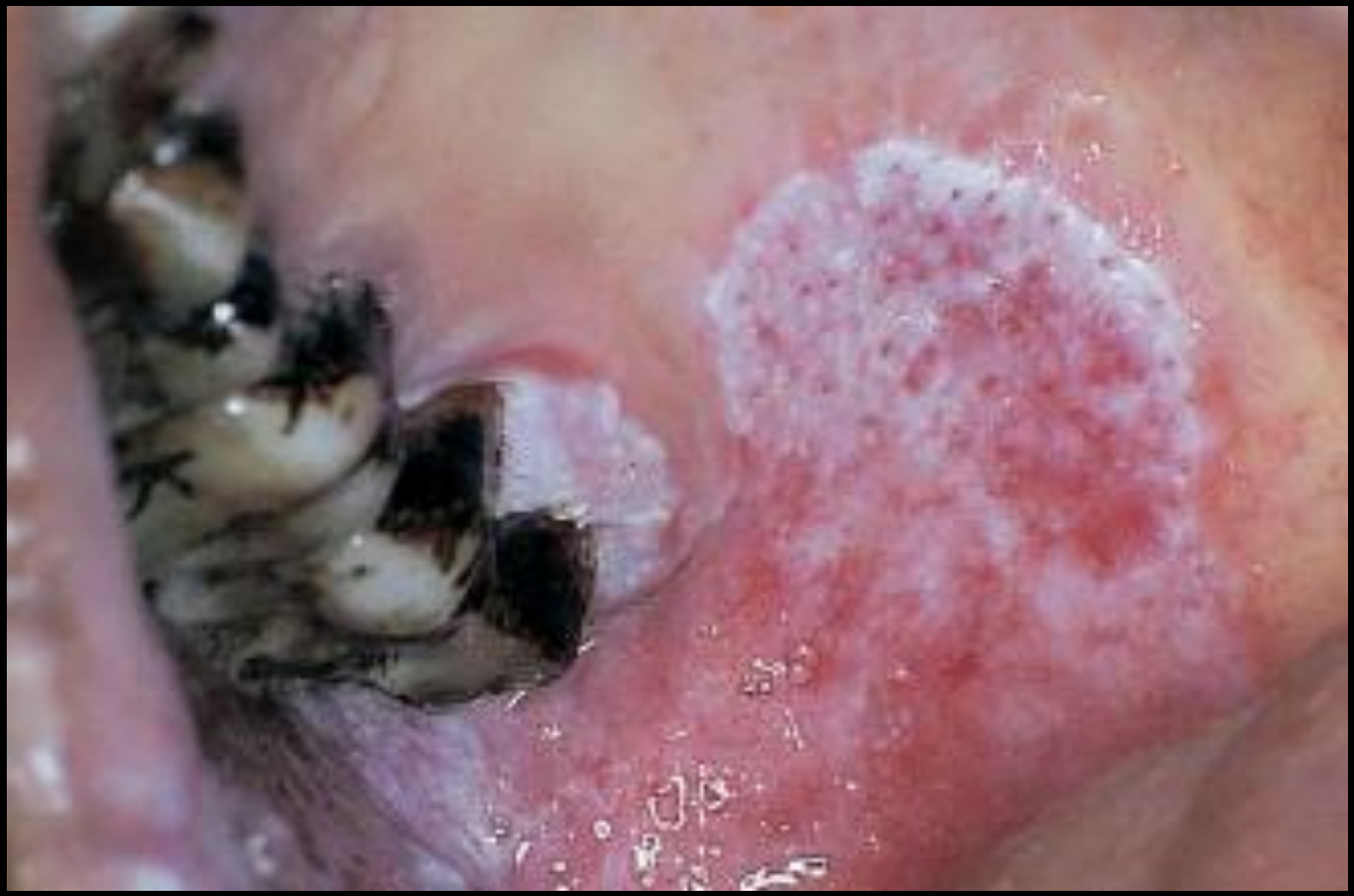


Histological appearance of PVL

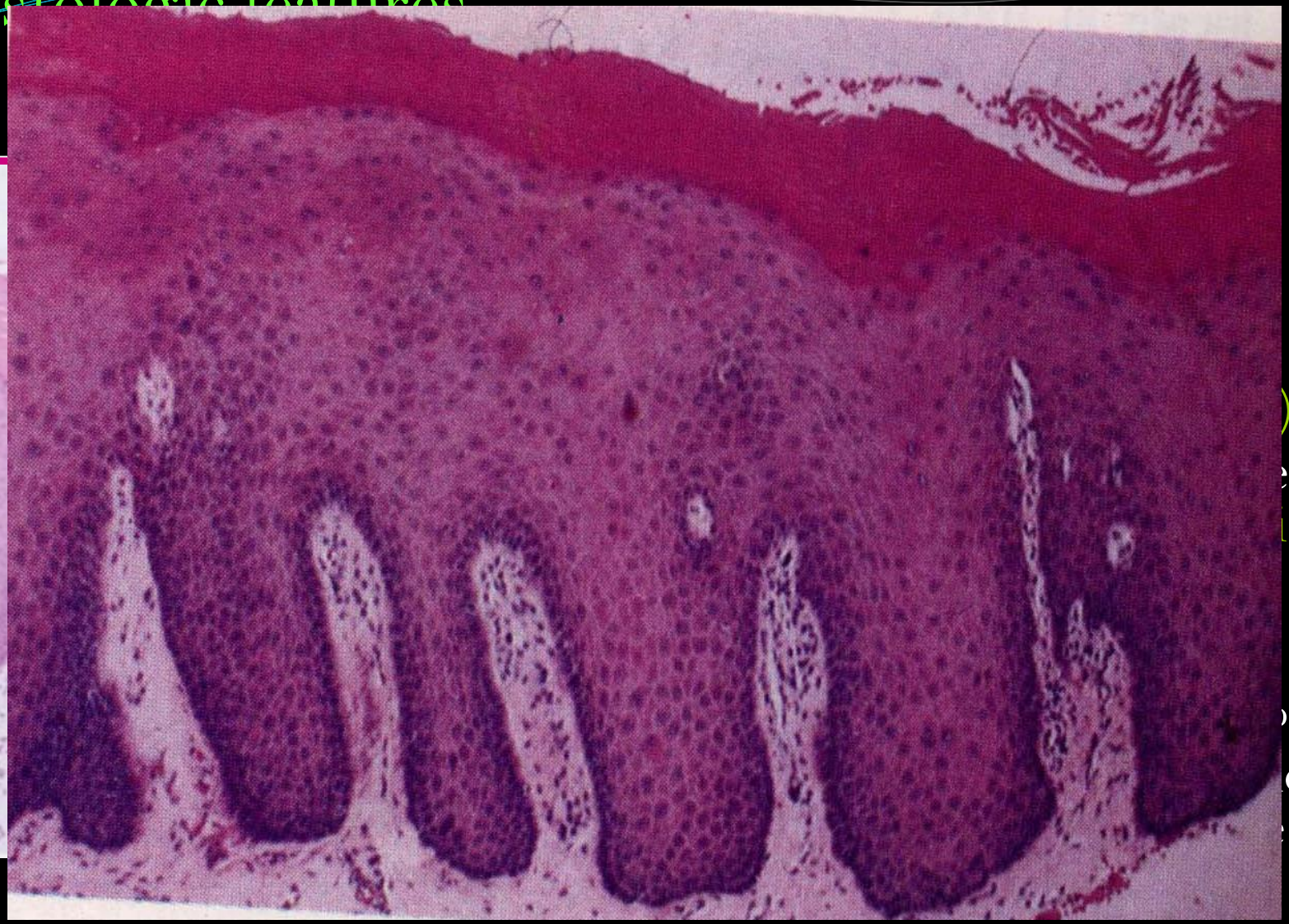




Erythroleukoplakia or
Speckled leukoplakia : scattered patches of redness



Histologic features



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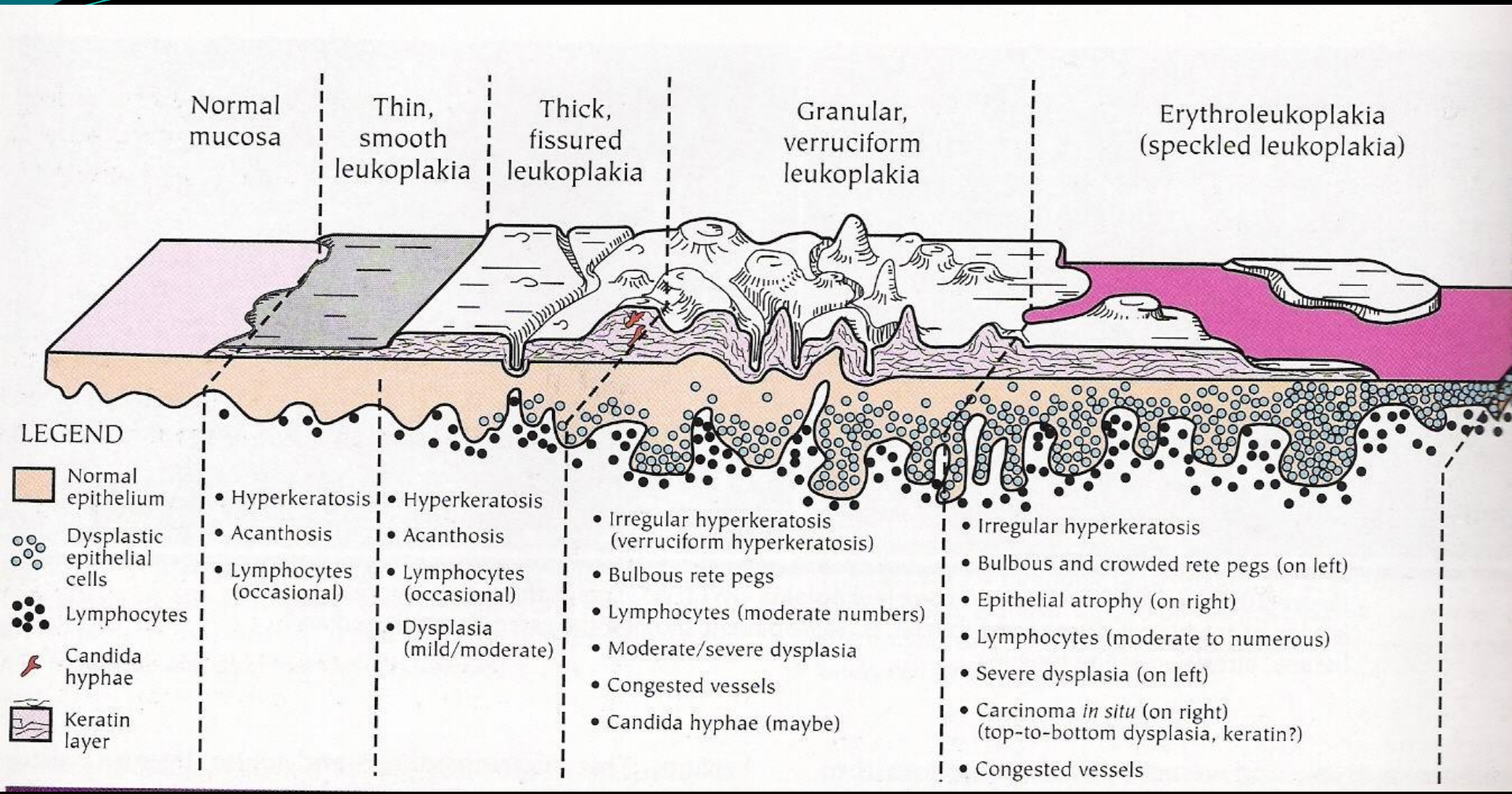


Sectional diagram of leukoplakia

High risk sites

- Erosions and ulceration are a clinical sign of malignant transformation
- 4-6% of leukoplakias progress to squamous cell carcinoma within 5 years
- high risk sites of malignancy:
  - floor of the mouth
  - lateral and ventral tongue
  - lips

Differential diagnosis

Nicotine Stomatitis

Candidiasis

Hairy Leukoplakia

Leukoedema

White sponge naevus

Fordyce granules

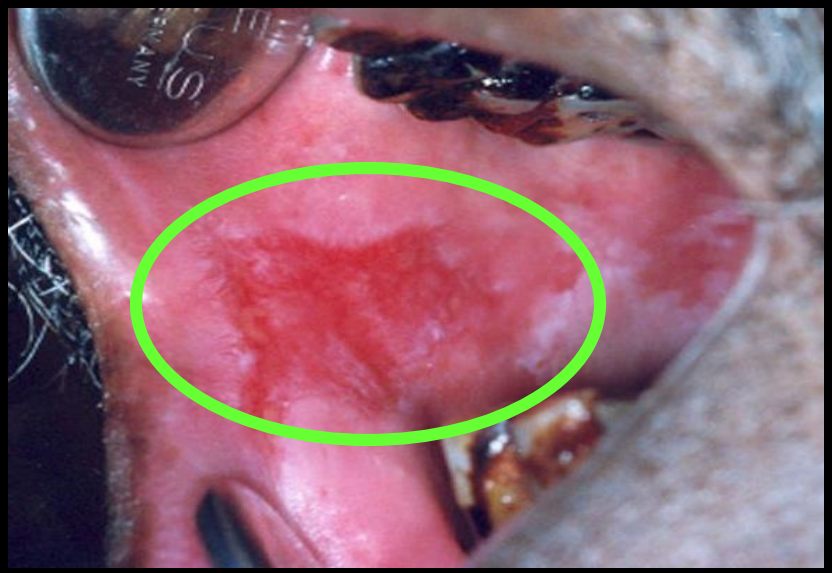
Erythroplakia

- " Any lesion of the oral mucosa that presents as a bright Red Velvety Patch or Plaque, which can not be characterized clinically or pathologically as any other recognizable condition."
- **Rare & always associated with dysplastic changes histologically**

Etiology : smoking , alcohol, candida infection

C/F: older age

- Floor of mouth , tongue & soft palate, corner of the mouth
- Erythematous soft area
- Smooth or nodular
- Asymptomatic or with burning sensation



H/F:

- Atrophic epithelium
- Lack of keratin formation
- The C.T. pegs extend very high into the epithelium and the capillaries in these superficial pegs are frequently quite dilated microvascular seen through epithelium -– red hue.
- C.T. - chronic inflammatory cell infiltration
- The vast majority of cases of erythroplakia are histologically either invasive epidermoid carcinoma, carcinoma in situ or severe epithelial dysplasia at the time of biopsy.

Intraepithelial carcinoma (ca in situ)

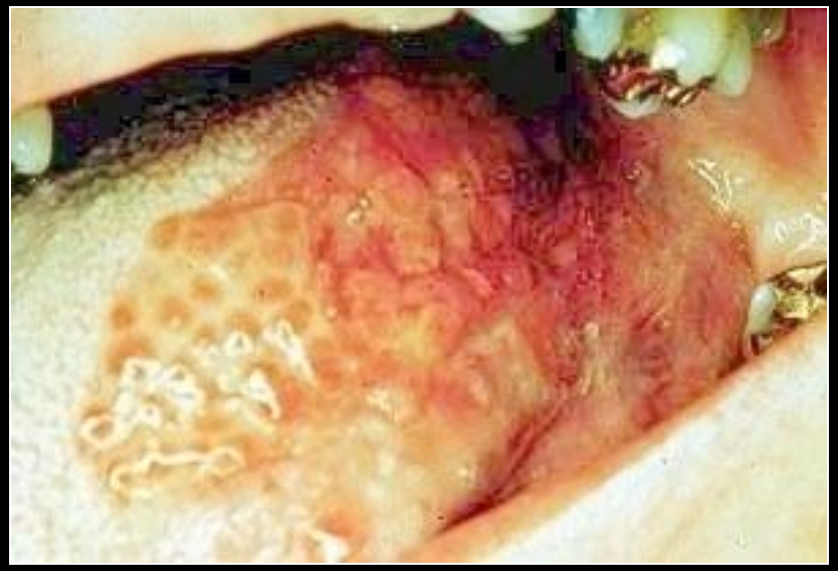
- Precancerous lesion
- Doesn't exhibit invasive malignant properties

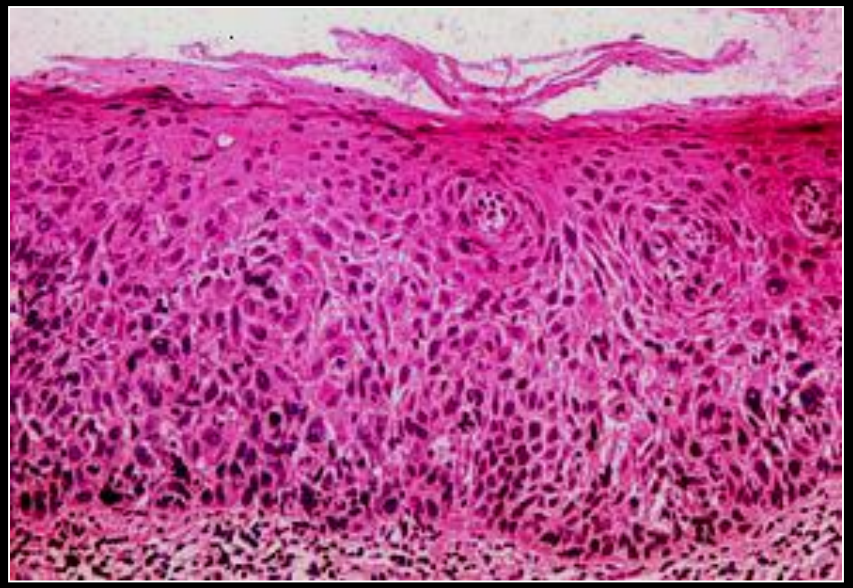
C/F: Leukoplakia or erythroplakia or combination of both or ulcer

- floor of mouth , tongue or lip

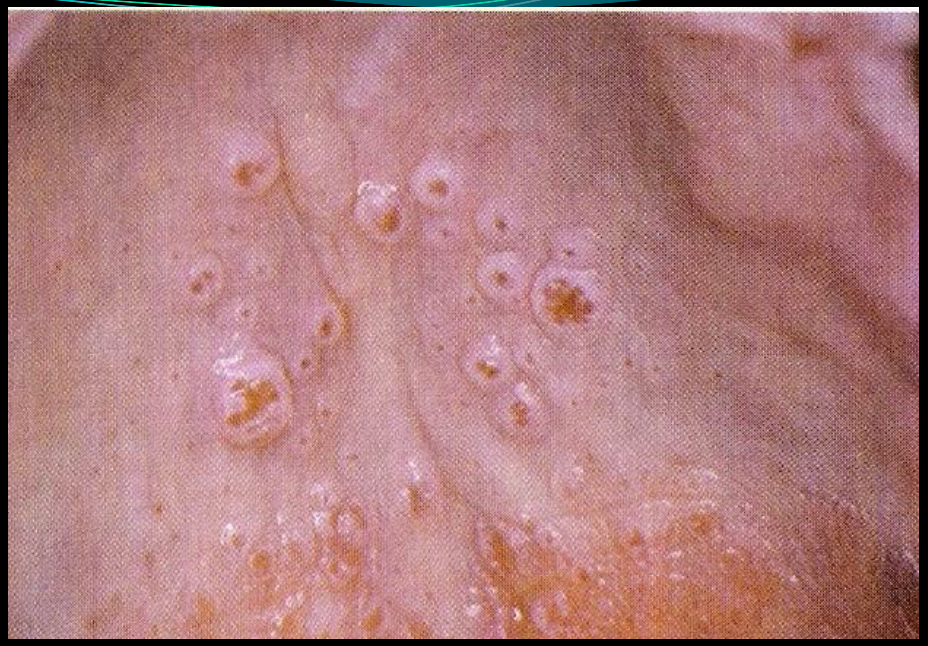
H/F:

- Epi. – hyperplastic or atrophic
- Keratin – may or may not present
- Cell keratinization or epithelial pearl formation rare dysplastic changes – top to bottom layers
- Basement membrane intact





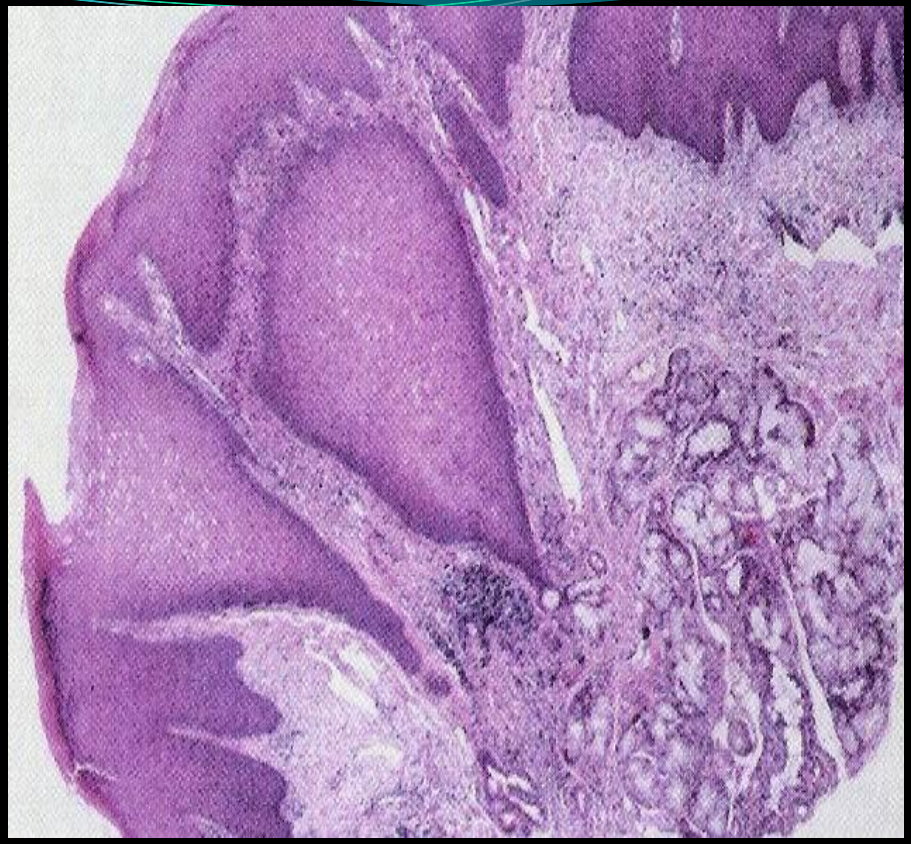
Stomatitis nicotina



- A specific lesion of the palate "stomatitis nicotina" (or "pipe smoker's palate") is seen frequently in persons who are heavy pipe smokers.

- It is first manifested by redness and inflammation of the palate which soon develops a diffuse grayish white, thickened, multinodular, or papular appearance with a small red spot in the center of each tiny nodule, representing the dilated and sometimes partially occluded orifice of an accessory palatal salivary gland duct, around which inflammatory cell infiltration is prominent.

- Fissures and cracks may appear, producing a wrinkled, irregular surface.
- The epithelium around the ducts shows excessive thickening and keratinization.
- This is regarded as simply an anatomic variant of leukoplakia.



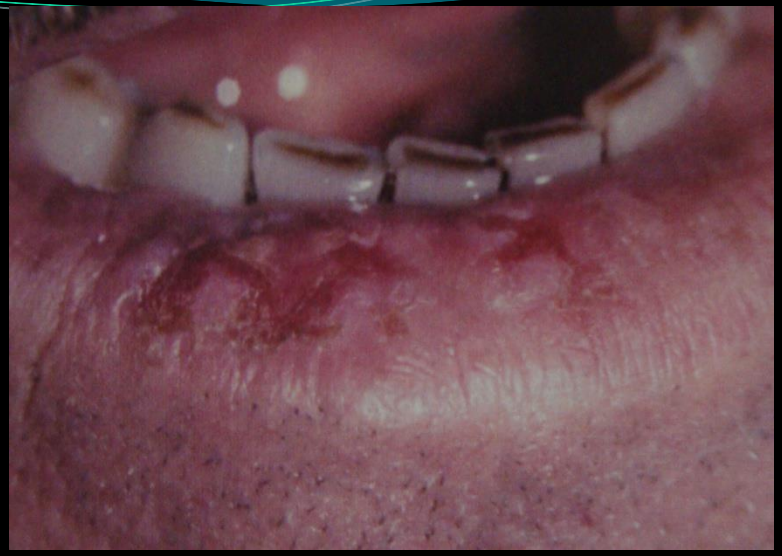
Thickening of epithelium & dilated orifices of minor salivary gland

Actinic cheilosis

- Premalignant alteration of lower lip vermillion
- Excessive exposure to UV rays from sunlight

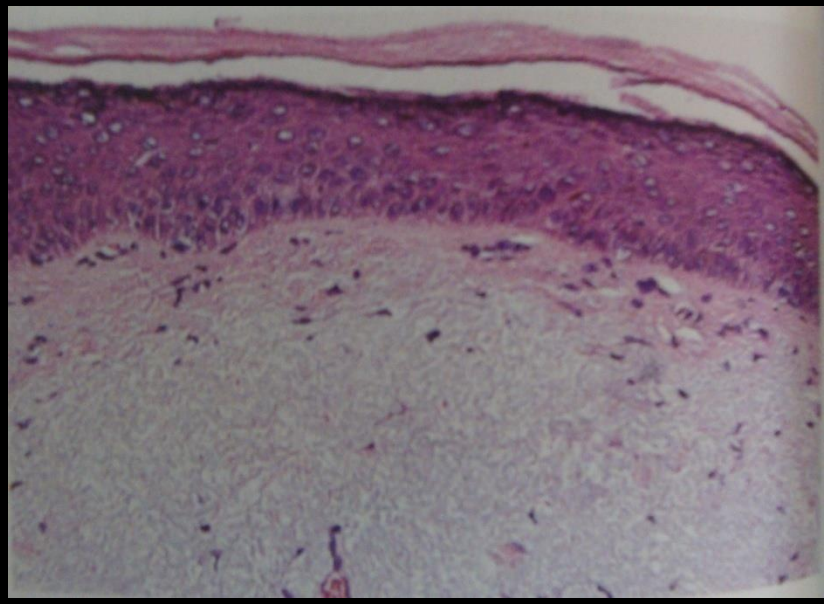
C/F: over age of 40 yrs

- Strong male predilection
- Atrophy of lower lip vermilion border
- Rough , scaly areas
- Crusted or ulcerated



H/F: atrophic st.sq. epithelium

- More keratin formation
- C.T. – amorphous basophilic changes
- Chronic inflammatory cells infiltration



H/F: atrophic st.sq. epithelium

- More keratin formation
- C.T. – amorphous basophilic changes
- Chronic inflammatory cells infiltration

Oral Submucous fibrosis (OSMF)

- Premalignant condition

- It occurs chiefly in southeast Asia, first reported in a group of East Indian women by Schwartz.

- Pindborg defined the disease as "**an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat**."

Etiopathogenesis :

- Clonal selection of fibroblasts with a high amount of collagen production during the long-term exposure to areca quid ingredients (Meghji et al, 1987).
- Stimulation of fibroblast proliferation and collagen synthesis by arecanut alk aloids (Harvey et al, 1986).
- By fibrogenic cytokines secreted by activated macrophages and T lymphocytees (Haque et al, 2000).
- By decreased secretion of collagenase (Shieh et al, 1992).
- Deficiency in collagen phagocytosis by OSF fibroblasts (Tsai et al, 1999).
- By production of collagen with a more stable structure (collagen type I trimer) by OSF fibroblasts (Kuo et al,. 1995).
- By stabilization of collagen structure by catechin and tannins from the areca nut (Scutt et al, 1987).
- By an increase in collagen cross-linkage as caused by upregulation of lysyl oxidase by OSF fibroblasts (Ma et al, 1995).

- The major areca nut alkaloids are arecoline, arecadine, arecolidine, guyacoline and guacine.
- The important flavonoid components in areca nut are tannins and catechins.
- These alkaloids undergo nitrosation and give rise to N-nitrosamine which may have cytotoxic effect on cells. (Hoffmann et al., 1994)
- Betel quid is placed in the buccal vestibule for ~15 min to 1 hr & repeated 5-6 times a day which leads to constant contact between mixture & mucosa.
- The alkaloids from the quid are absorbed into the mucosa and undergoes metabolism.
- Microtrauma produced by the friction of coarse fibers of areca nut also facilitates diffusion of the alkaloids into the subepithelial connective tissue resulting in juxtaepithelial inflammatory cell infiltration. (Chiang et al., 2002).

ROLE OF ARECOLINE

Arecoline

(Slaked lime) (Hydrolysis)

Arecaidine

Fibroblast stimulation & proliferation

Increased collagen synthesis

Stabilization of collagen by tannins (and catachins polyphenols)

Large quantity of **tannin** present in areca nut

↓ Inhibits collagenases

Reduced collagen degradation

Arecoline + tannin → ↓ degradation of collagen
↑ production of collagen

Presence of Copper in nut:

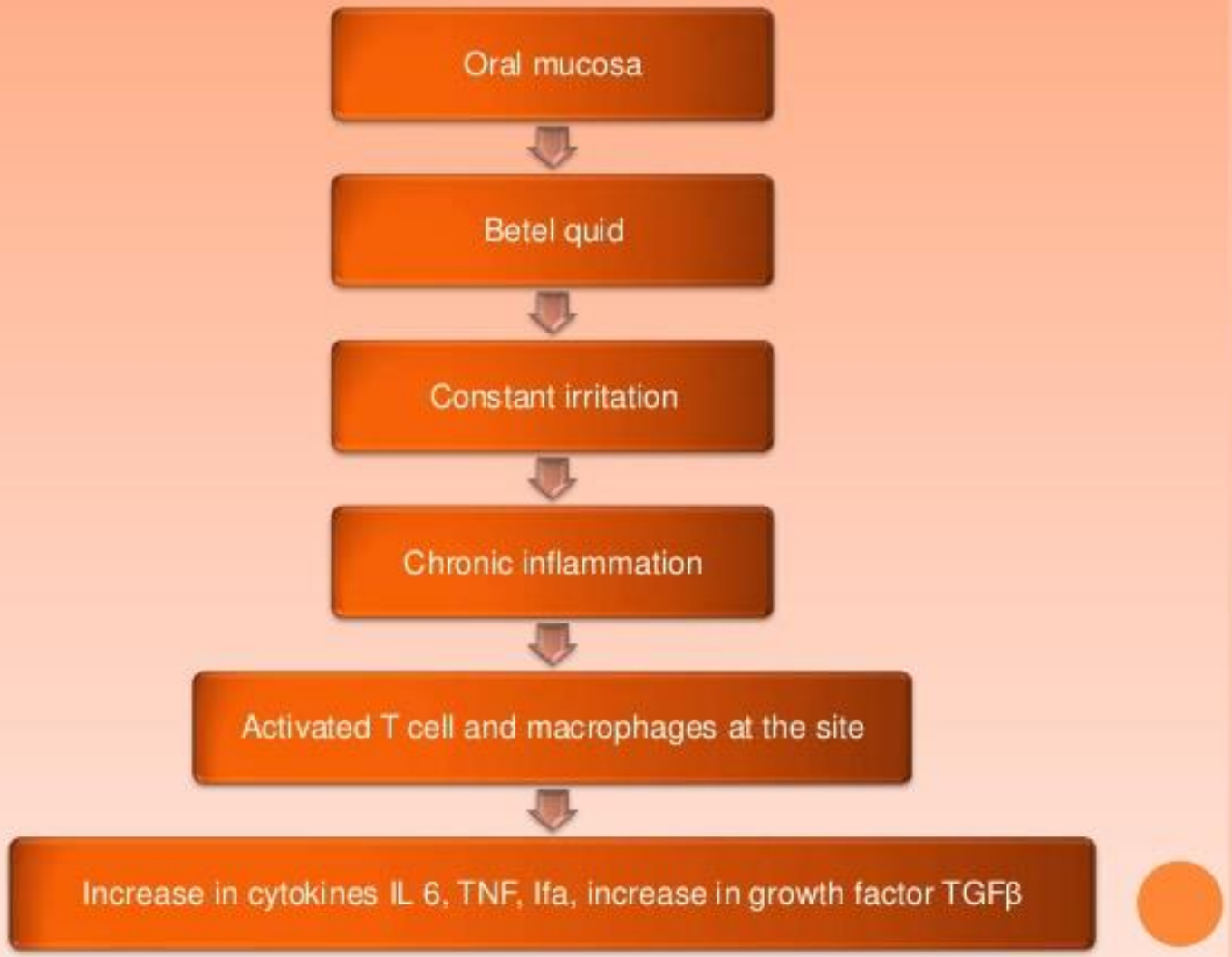
Copper content in areca nut

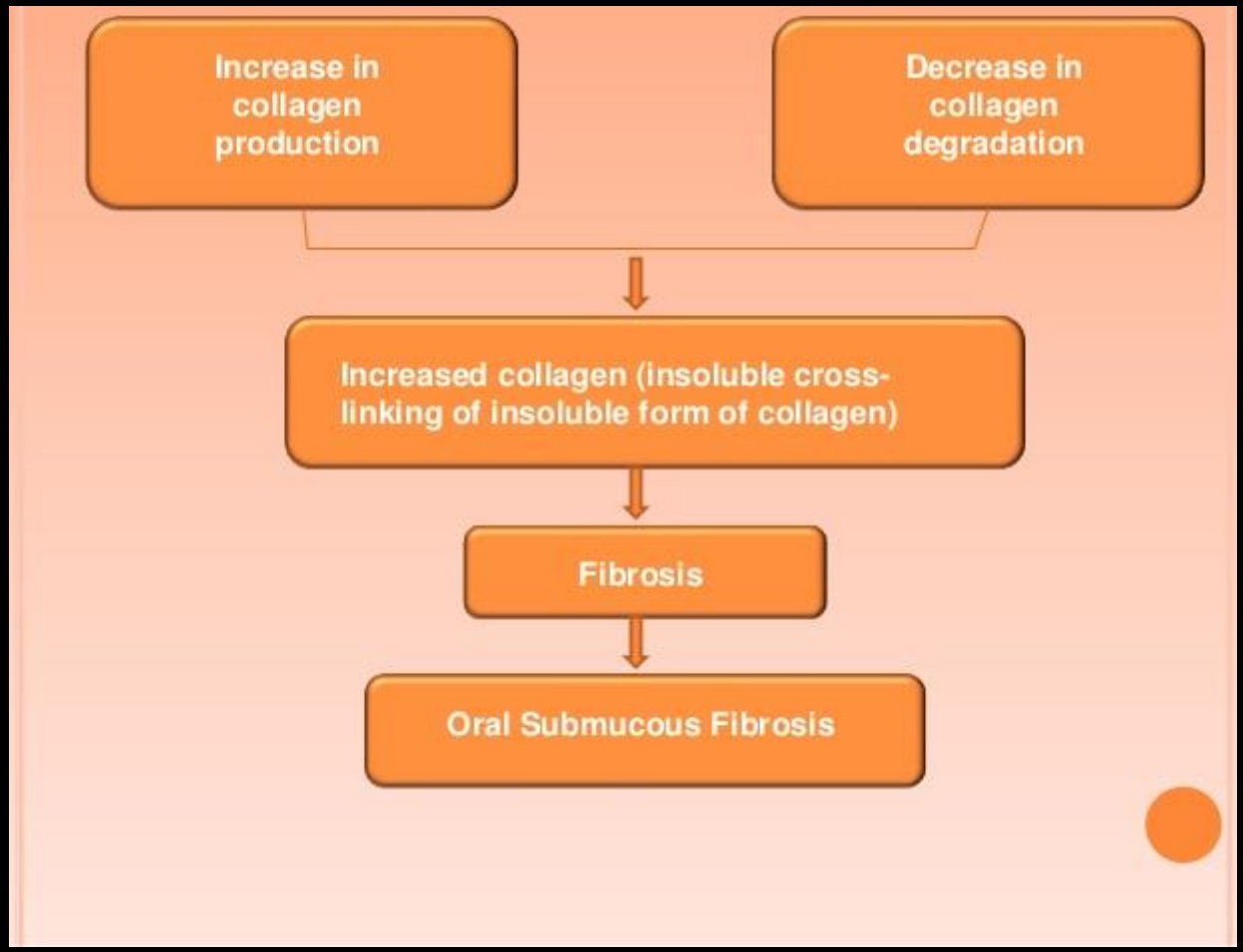
↓ (Increased activity of lysyl oxidase enzyme)

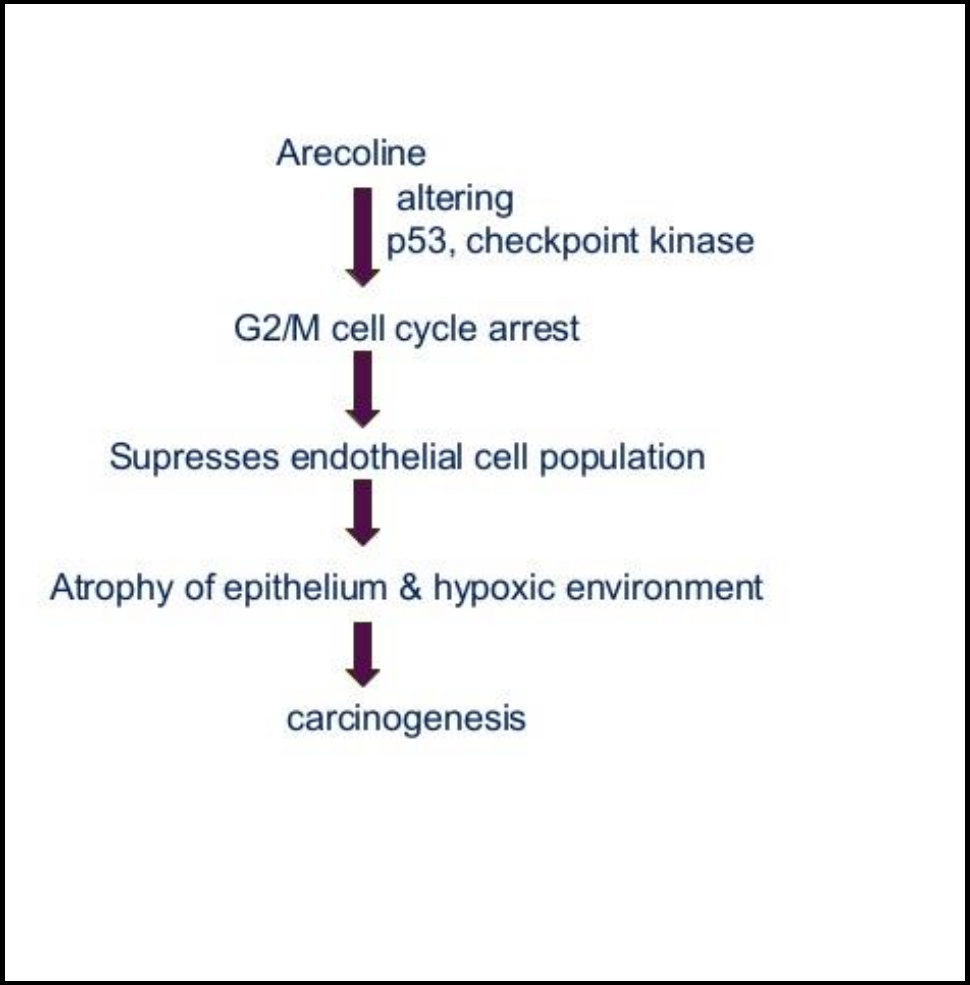
Fibroblast stimulation & proliferation

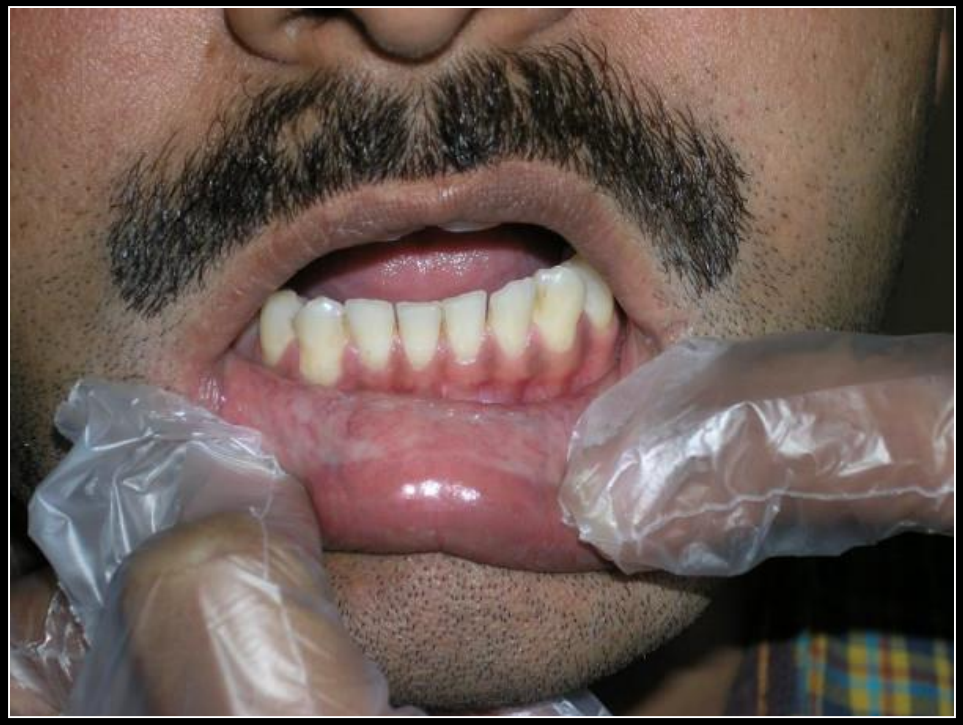
↓

Increased collagen synthesis


Oral mucosa
Betel quid
Constant irritation
Chronic inflammation
Activated T cell and macrophages at the site
Increase in cytokines IL 6, TNF, Ifa, increase in growth factor TGFβ


Increase in collagen production
Decrease in collagen degradation
Increased collagen (insoluble cross-linking of insoluble form of collagen)
Fibrosis
Oral Submucous Fibrosis

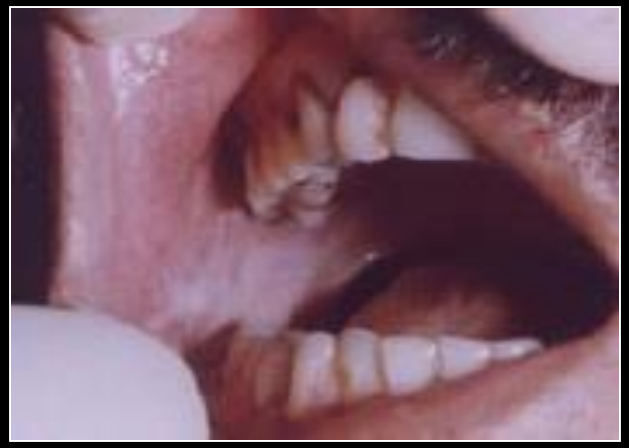

Arecoline
altering
p53, checkpoint kinase
G2/M cell cycle arrest
Supresses endothelial cell population
Atrophy of epithelium & hypoxic environment
carcinogenesis

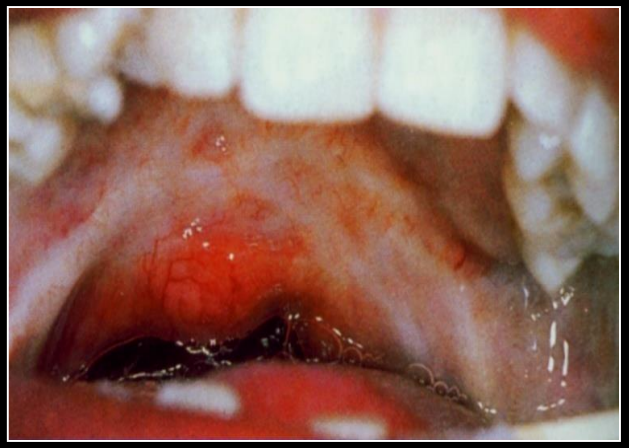


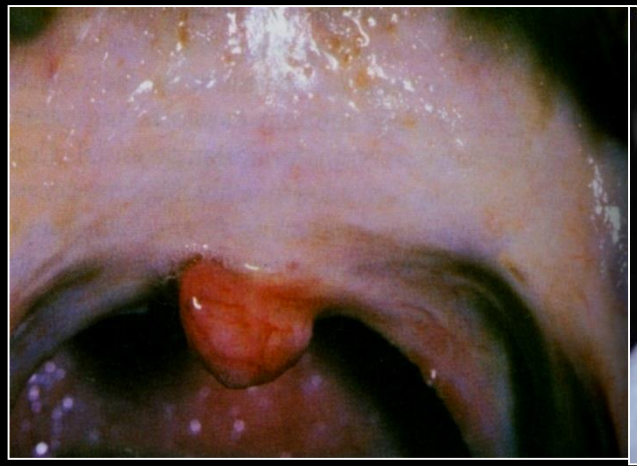
C/F:

- insidious (developing gradually as to be well established before becoming obvious): 2-5Yrs
- early symptoms: burning sensation, blisters on palate – ulceration or generalized inflammmation of mucosa

- Fibrous bands : vertical direction and involve Buccal mucosa, retromolar area, soft palate
- Mucosa appears blanched
- Inability to open mouth
- Impairment of tongue movement
- Stiffening : difficult swallowing

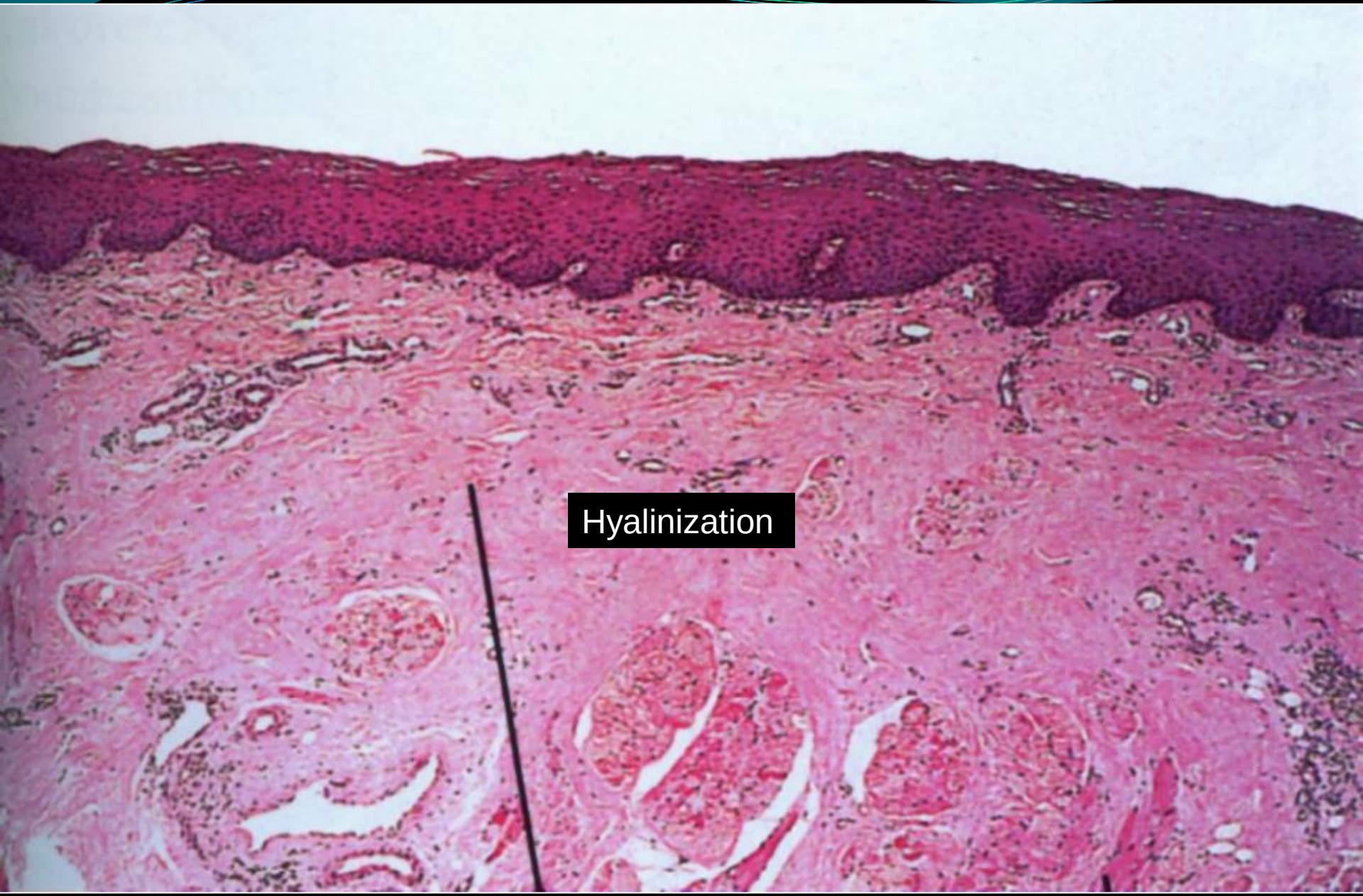


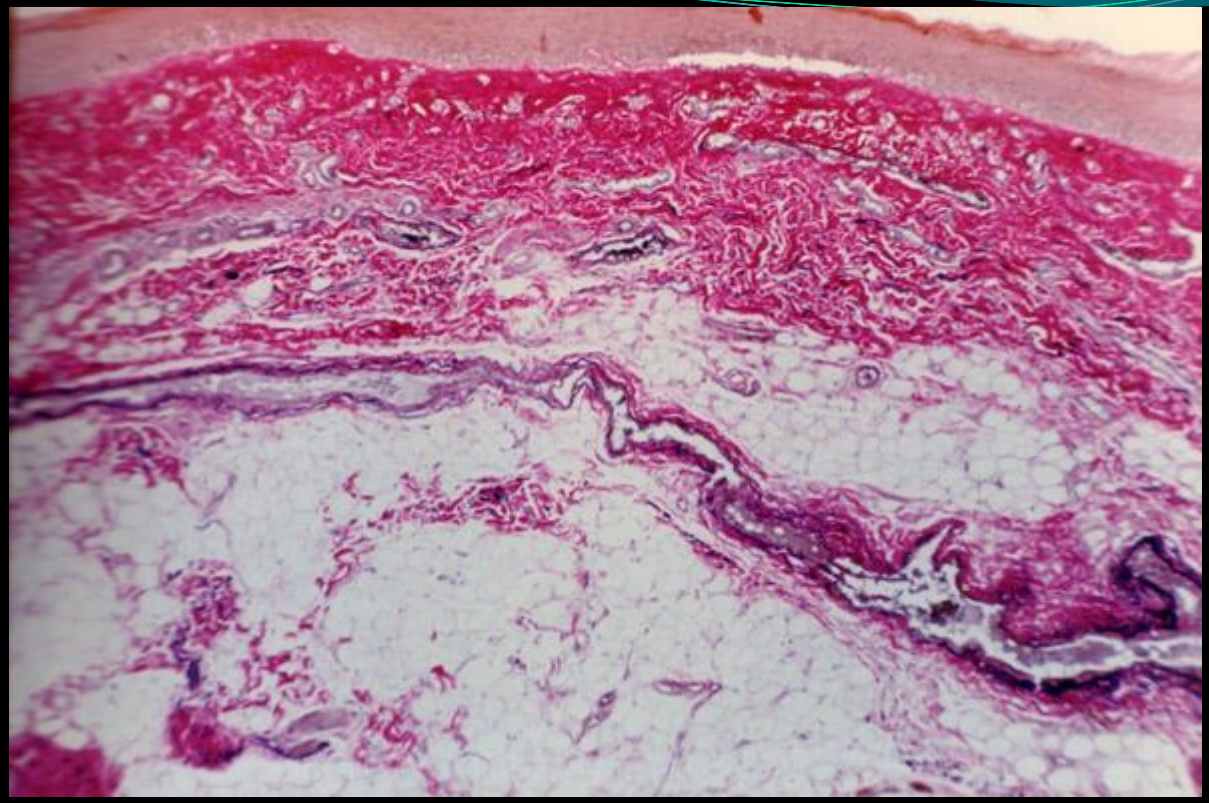




Figs 3A and B: Oral submucous fibrosis associated with (A) oral leukoplakia, (B) oral malignancy

Submucous fibrosis





ORAL SUBMUCOUS FIBROSIS:

Advanced stage with fibrosis of lamina proporia

Van Gieson stain (collagen-red)

WHITE LESIONS

- Hereditory conditions:
    1) Leukoedema
    2) White sponge nevus
    3) Hereditory benign intraepithelial dyskeratosis
- Reactive lesions:
    1) Focal (frictional) hyperkeratosis
    2) Nicotine stomatitis
    3) Hairy leukoplakia
    4) Hairy tongue
- Preneoplastic lesions:
    1) Leukoplakia
    2) Actinic chelitis
- Other white lesions:
    1) Submucous fibrosis
    2) Geographic tongue
    3) Lichen planus
    4) Lupus erythematosus
- White – yellow lesions
    1) Candidiasis
    2) Mucosal burns
    3) Fordyce's granules
    4) Gingival cyst
    5) Parulis
    6) Lipoma