REVIEW OF LITERATURE
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HISTORICAL BACKGROUND OF ORAL CYTOLOGY

The interest of oral exfoliative cytology dates back to 1843 when Walshe first microscopically detected tumour particles in the sputum of a patient.

The first attempt at the cytologic diagnosis of pharyngeal cancer by oral smear was made over a century ago, in 1860, by Beale.

Hampelin in 1876 and Betechardt in 1895 contributed additional observation of malignant cells in the sputum of patients with carcinoma of the pharynx, lungs and bronchi.

The first modern application of oral cytology was that of Morrison and co-workers in 1949, who used the smear technique to diagnose nasopharyngeal lesions. They concluded that (i) the results were excellent, (ii) the procedure was not a substitute for biopsy, (iii) the technique was a valuable adjunct and positive results demands that the source be sought, (iv) a knowledge of normal cytology is essential, (v) strict attention must be paid to detail and (vi) that cytologist must be experienced to evaluate the oral smear. These conclusions, certainly are still true today.
In 1943, Papanicolaou and Traut published their technique of staining the cells for proper and correct identification and study. Since the publication of Papanicolaou’s staining technique, exfoliative cytology came to be recognized as a reliable diagnostic tool specially in identifying early cancers in different sites and effusions.

Montgomery (1951) studied the oral cytology of normal patient and emphasized the degree of variation that can be seen in the absence of disease.

Miller and Co-workers (1951) reported differences in the degree of cornification of oral mucosa depending on its anatomical location and Peters (1954) described the different cell types found in oral smears.

Several workers (Pomeranz and Stahl, 1953; Wahl and Gupta, 1954) applied this technique to known or clinically suspected oral carcinoma, to study its usefulness and to study different types of cells present in oral cytology.

Criteria for the interpretation of malignancy in oral smears have been listed by several investigators (Cawson, 1960; Hopp, E.S., Montgomery and Haam, 1951; Peters, H. and Rijssinghani, 1956).
Various methods were tried to collect a suitable specimen for study. Gladstone and Kidney (1950) used both gelfoam and cellulose sponge to collect specimen of representative cells. Montgomery (1951) used Woodson's No.2 metal plastic instrument and Pomeranz and Stahl (1951) used a wooden spatula to scrap the lesion and got satisfying results. Hopp (1958) however, found the tightly wound cotton applicator to be a handy as well as simple tool to collect specimen by firmly rubbing over the lesion and adjacent areas. Helsper, Sharp and Bullock (1963) presented the mouth wash technique to screen for intra oral carcinomas by which it was possible to get representative cells from all parts of the oral cavity. Scheman, Lumerman and Alchuler (1968) introduced 'Cytoaspirator' an instrument of their own design, for deep suction abrasion method of cytologic sampling. Malberger (1974) used aspiration biopsy to collect specimen from deeply seated orofacial masses. Camillert (1968) remarked exfoliative cytology to be an established method in the diagnosis of neoplastic and non-neoplastic lesions of the oral cavity. However, cent percent diagnostic accuracy has not been established by this method.

THE NORMAL ORAL MUCOSA

Knowledge of normal conditions is the prerequisite for diagnosis of pathological changes. The normal mucosa presents a moist, glistening surface, and is a rose
or greyish-pink colour due to the vascular bed in the connective tissue underlying the epithelium being well supplied with blood. The movability of the oral mucosa varies, and distinction is made between locolabile (lip, cheek, tongue, floor of mouth) and locostable (hard palate, gums) areas (Table - 1).

Table - 1 : Histological structure of the Oral Mucosa

<table>
<thead>
<tr>
<th></th>
<th>Locolabile mucosa</th>
<th>Locostable mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stratified epithelium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal layer</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prickle-cell layer</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Granular layer</td>
<td>-</td>
<td>+/(+)</td>
</tr>
<tr>
<td>Horny layer</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>Orthokeratosis (Anucleate)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Parakeratosis (Nucleate)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>rete pegs/connective tissue</td>
<td>Shallow</td>
<td>deep</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>wide, loose</td>
<td>narrow, fibrous</td>
</tr>
<tr>
<td>Occurrence</td>
<td>lip, cheek, tongue, floor of mouth</td>
<td>palate, gingiva</td>
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Histological examination shows the surface to be covered with a stratified squamous epithelium, with the sequence of layers similar to that seen in the epidermis of the skin. A basal cell layer (Stratum basale), spinous layer (Stratum spinosum) and flattened horny layer (Stratum corneum) may be distinguished. A granular layer (Stratum granulosum) is found only in areas showing orthokeratotic keratinisation. However, as a rule, there is clearly less keratinisation than in the epidermis. Differentiation is made between orthokeratosis, with a granular layer and anucleated squames, and parakeratosis, with nucleated squames. The degree and type of keratinisation show considerable variation (Table 1). In areas not subject to much mechanical stress, such as the cheek, parakeratosis is frequently only demonstrable with special staining techniques, while areas subject to mechanical stress, such as the gums and the hard palate, show orthokeratosis like the epidermis. Particular structural elements in the epithelium are the attachment plaques, or desmosomes. These provide mechanical intercellular cohesion and are responsible for the appearance of 'prickle' cells. The tonofibrils, which act as an 'internal skeleton', and the keratin produced from them afford mechanical protection. Their quantity and density determine the translucency of the epithelial layer and hence the macroscopic coloration.
of the mucosa. Increased keratinisation, as in the epithelial hyperplasia known as leukoplakia and in hyperkeratosis, causes the rosy tinge of the mucosa to give way to the naturally whitish colour of the epithelium. Decreased keratinisation e.g. in dystrophic epithelial atrophy, causes dark red discoloration of the mucosa (erythroplakia).

The interdigititation of epithelium (rete pegs) and connective tissue (papillae) also shows considerable variation, being more marked in areas subject to greater wear and tear. The subepithelial connective tissue contains a dense network of capillaries that supply it with blood, and is richly innervated. The muscularis mucosae, which in other mucous membranes separates the lamina propria from the underlying connective tissue is absent.

Both the epithelium and subepithelial tissues contain cells with nonspecific defensive functions (leukocytes) and immunocompetent cells conferring local immunity (lymphocytes and plasma cells in subepithelial tissues; lymphocytes, cerebriform lymphoid cells and Langerhan's cells in the epithelium). The specialised structure of the dorsum of the tongue is well known, and only brief reference need be made to the numerous fine filiform papillae, the scattered fungiform papillae, and the limited number of
vallate papillae arranged at the junction between the anterior two third and the posterior third. In the lateral parts of the posterior third, the presence of lymphoid tissue gives an irregular or nodular appearance.

**PRE-MALIGNANT ORAL LESIONS**

The term "Precancerous lesion" has been used to signify clinical and/or pathological entities related to cancer development either as a result of prospective study of the progression of such lesions to cancer or a retrospective study of occurrence of such lesions with cancer. In the words of Kramer (1976), "For all practical purposes, a condition may be termed 'precancerous' if it is believed that the risk of malignant change is sufficiently high to influence the management". In the oral cavity various lesions have been described as precancerous. These are leukoplakia, submucous fibrosis, melanoplakia, erythroplakia, oral lichen planus, papilloma and Plummer Vinson's syndrome.

1. **LEUKOPLAKIA**

   Literally the word means a 'white patch'. This is defined as a white patch or plaque on the mucosa that can not be rubbed off and is not ascribable to any other condition (WHO Collaborating Centre for oral pre-cancerous lesions, 1978).
Aetiology and prevalence:

Leukoplakia is said to be associated with various factors such as poor diet, poor oral hygiene, local irritant such as caries, irritation from a badly fitting denture or a broken tooth, oral sepsis, syphilis, tobacco, alcohol, vitamin deficiency, endocrine disturbances, galvanism and actinic radiation in the case of leukoplakia of lips.

Its correlation with the use of tobacco is of particular interest in India where the prevalence and localization of oral cancer have already been shown to be correlated with the use of tobacco (Cox, 1933; Sanghvi et al, 1955; Wahi et al, 1955; Hiraigama, 1966).

The aetiology has got a definite relation with smoking specially in combination with chewing of 'Pan' or 'Betel-nut' (Sughr et al, 1969; Bhonsle et al, 1976; Silverman et al, 1976). Gurry et al (1952) found leukoplakia among 0.2% of 2004 inhabitants, 41% of whom were betel-nut chewers.

Out of 36 cases of leukoplakia studied by Cook (1951), 13 were considered to be related to smoking, 18 were considered to be caused by frictional irritation, and 3 were associated with syphilis.
In India Mehta et al. (1961) examined 4734 men of the Bombay police and reported 3.4% or leukoplakia. 76.5% of the men gave history of pan chewing, bidi/cigarettes smoking or had both of these habits. The prevalence of leukoplakia was higher among tobacco users (4.5%) than among non-users (0.09%) and higher among those who either chewed pan (4.2%) or smoked bidi (3.7%). The leukoplakia is common in older age group (Waldron et al., 1975; Silverman et al., 1976). The incidence is slightly more in males than in females. Incidence of malignant changes is more as age advances (Cawson, 1969).

Common sites of occurrence of leukoplakia are buccal mucosa (Silverman, 1976). According to Penstrup (1958) buccal mucosa and commissures were most frequently involved, followed in descending order by the alveolar mucosa, tongue, lip, hard and soft palates, floor of the mouth and gingiva. In the study of Shafer and Waldron (1960) the greatest number of cases in both men and women occurred on the mandibular alveolar ridge, gingiva or mucobuccal fold. Shab et al. (1961) reported that the buccal mucosa was most frequently involved followed in descending order by along the interocclusal line, angle of mouth, related to last molar tooth, tongue, gums, palate and lips.
Cytological study of leukoplakia:

Exfoliative cytologic studies in oral leukoplakia were first performed by Montgomery and Von Hamm (1951).

Peters and Fijshinghani (1956) studied smears of oral leukoplakia and stated that these smears varied considerably in their cell count, some showing a profuse desquamation of cornified, superficial squamous cells and large number of keratinized cells while other smears showed a varied cell population and considerable cell atypia. Although they were not able to analyze whether the two different smear types could be correlated with the stage of the disease, they were under the impression that early cases of leukoplakia showed the uniform smear type while advanced cases of leukoplakia showed cells of great variation.

According to Sandler and Stahl (1958) oral cytologic technique was well suited for the follow-up of chronic oral lesions such as leukoplakia; yet, in the same year Silverman, et al. (1958) stated that "unfortunately, suspicious areas of intra-oral leukoplakia prior to fissuring or ulceration, do not lend themselves readily to the cytologic smear method, since only superficial cornified cells are obtainable in smears taken from these white patch areas. They found
no diagnostic chance in smears scraped from the nine cases of 'leukoplakia' and stated that leukiplakia remains a diagnostic enigma prior to histopathological examination.

Smears from leukoplakia exhibited acidophilic cytoplasm in approximately 75% of the superficial cells along with cells having pyknotic nuclei and anuclear cells (Wahi and Gupta, 1954).

Umiker et al (1960) reported cytologic atypism in smears from 9 of 45 patient with clinical oral leukoplakia.

Wahi and Luthra (1966) had studied the oral scrape of patients of leukoplakias and reported three types of cellular pattern. First - Simple leukoplakia-associated with ortho-keratotic type of epithelium, smears were showing abundant exfoliation of denucleated superficial cells. The nucleated superficial cells encountered showed minimal amount of nuclear atypism. The second type of smears was accompanied by a parakeratotic type of epithelium, presenting a picture of active leukoplakia with exfoliated cells showing varying degree of nuclear atypism. The third pattern showed a smear with combination of the above two.
Generally, in cases of leukoplakia, the exfoliation of superficial cells pre-dominated the intermediate and basal cells being infrequent. Inflammatory cells are usually abundant and in clumps. Cytoplasmic granulation, vacuolation and peri-nuclear haloes are seen. Macro-nucleoli are observed more frequently. Intermediate and basal cells are seen isolated or in small groups. The cytoplasm is basophilic in most of these cells. An occasional case of leukoplakia with marked cellular atypism shows the exfoliation of one or two benign epithelial pearls.

Shklar et al (1968), Debelsteen et al (1971) do not recommend cytological study from surface smears to determine the pre-malignant nature of leukoplakia. However, Lahiri et al (1974) and Sahijar et al (1975) found the cytological study from surface smears quite an useful method to surveillance for the diagnosis of malignant change in this condition.

**Histological study of leukoplakia**:

Histologically, leukoplakia, usually show some hyperkeratosis. Commonly there is a epithelial hyperplasia and diffuse chronic inflammatory cells infiltration in the lamina propria. From prognostic point of view special attention is given to epithelial dysplasia. Marked epithelial dysplasia is a fairly reliable indication of impending serious change.
Iwasaki et al (1988) classified leukoplakias into four groups based on histopathological characteristics.

- **Group I** - Epithelial hyperplasia
- **Group II** - Superficial keratosis
- **Group III** - Combination of hyperplasia and keratosis.
- **Group IV** - Epithelial dysplasia

Based on clinical approach Banoczy et al (1972) divided lesions into leukoplakia simplex (having keratinized mucosa), leukoplakia verrucosa (having verrucous proliferation) and leukoplakia erosiva (ulcerated leukoplakia). The type of keratinization varied according to clinical appearance; hyper ortho-keratosis was found in the majority of leukoplakia simplex and verrucosa and hyperparakeratosis was found in the leukoplakia erosiva cases. They found 12.2% malignant change in erosive, 32% in verrucous leukoplakia and none in simplex leukoplakia group.

II. **OPAL EPITHELIAL FIBROSIS**

Submucous fibrosis of the oral cavity, a chronic disease of insidious onset and unknown etiology, endemic in India, not seen in the Western countries nor described in literature (The only reports
from other countries are those of Schwarts (1952) who described the entity in Indians settled in East Africa and Su (1954) from Taiwan) is prevalent throughout the Indian subcontinent sparing no caste and creed, affecting the young and the old, the rich and poor alike. The disease is characterised by the presence of palpable fibrous bands in the oral submucosa which may ultimately lead to severe restrictions of the movements of the mouth including that of the tongue.

There was controversy regarding the terminology of the disease. To refer back to our own history of ancient medicine Sushruta in his classification of mouth and throat maladies mentioned a condition 'VIDARI' similar to sub mucous fibrosis (cited by Mukherjee and Bierwan 1972). In the modern literature this condition was first reported by Schwartz (1952) in a group of East Indian women residing in Kenya, East Africa as 'atrophia idiopathica (tropica) mucosae oris'. In India it was first described by Joshi (1953) as submucous fibrosis of the hard and soft palate and pillars. Other names that have been suggested are 'diffuse oral submucous fibrosis' by Lal (1953), 'idiopathic scleroderma of the mouth' by Su (1954), 'idiopathic palatal fibrosis' by Rao (1962) and 'sclerosing stomatitis' by Bohr (1962) and 'Juxta epithelial fibrosis' by Findlay (1966). The term 'oral sub mucous fibrosis' is now widely accepted.
Geographical Distribution

Oral sub mucous fibrosis has been recorded mainly amongst Indians but occasional cases have been reported from Taiwan (Su, I.P., 1954), Nepal, Thailand, South Vietnam and Ceylon (Pindborg and Sircat, 1966). Among Indians living outside India submucous fibrosis has been found in Malaysia (Pindborg and Sircat, 1966), Uganda (Miller, 1965) and South Africa (Dockrat and Sheer, 1964). Isolated cases among Pakistanis and Indians living in the United Kingdom have also been reported (Kees and Madan, 1968). Furthermore, oral submucous fibrosis (OSMF) has been diagnosed among domiciled European living in Hyderabad and a British female living in England and married to a Pakistani (Simpson, 1969) Dockrat and Sheer (1969) examined 1000 Indians in South Africa and found a prevalence of 0.3%.

In India oral sub mucous fibrosis cases have been reported from different regions - from Madhya Pradesh (Lal, 1952); Bombay (Joshi, 1953; Desa, 1957); Bihar (Sharan, 1959); Hyderabad (Rao, 1962) and from Gorakhpur, Uttar Pradesh (Gupta et al, 1978).

Prevalence and Incidence

Epidemiological studies on prevalence of oral sub mucous fibrosis have been carried out by various
investigators, Pindborg et al (1964) examined 35,000 urban Indians seeking admission in clinics at Dental Colleges in Lucknow, Bombay, Bangalore and Trivandrum and found the prevalence of 0.5%, 0.5%, 0.2% and 1.2% respectively. The prevalence rate in Southern India is found to be more (Pindborg et al, 1964; Wahi et al, 1966; Mehta et al, 1971). Pindborg (1980) has estimated that not less than 2,50,000 cases of oral sub mucous fibrosis (OSMF) are present in India. Varghese et al (1986) have found an increased prevalence of OSMF in the cashew workers of Kerala (7.85%).

Reports of sex ratio vary, however the majority demonstrate a female predominance (Schwartz, 1952; Rao and Raju, 1954; Rao, 1962; Wahi et al, 1966; Pindborg et al, 1968). The largest number of cases occur between the ages of 20 and 40 years (Wahi et al 1966, Zacharias et al 1966 and Mehta et al, 1971). DeSa (1957) and Sirsat and Khanolkar (1962) found a nearly equal distribution of cases among males and females. Sharan (1959), Su (1954) found a predominance of males in their study.

Aetiological Factor

The exact aetiology is not yet established. Phatak (1978) found significantly elevated levels of globulins and immunoglobulins and suggested it to be
an autoimmune disease. Various causative factors have been mentioned such as chewing of tobacco, betel nut, pan and pan masalas, eating of spices and chillis, hereditary predisposition, Vitamin A and B complex deficiency, localised collagen disease and reaction to bacterial infection etc.

**Tobacco, Betel nut, Pan and Pan Masalas chewing**:

The chewing of betel quid is mentioned in the Sanskrit 'Sushruta Samhita' believed to have been written about 600 A.D., near Benaras (Varanasi). The Sanskrit for the leaf of betel vine 'Tambula' persists in the modern Hindi 'Tambuli' and in the Arabic and Persian 'Tambula'.

The role played by tobacco is debatable as submucous fibrosis had occurred in patient who had never indulged in tobacco habits (Paymaster 1956). Betel nut chewing causes degenerative changes in connective tissue of oral mucosa followed by fibrosis (Sharan, 1950; Lal, 1953 and Lemonor and Shear, 1969). The disease according to 
Su (1954) in the betel nut chewers may be caused by-

(i) Amount of tannic acid (14 to 18%)

(ii) Influence of alkali lime

(iii) Continued and prolonged action of alkaloid arecoline on nerve ending and consequent neuroatrophic seodrants.
According to Findborg (1965) the most important etiological factor for producing oral submucous fibrosis and oral cancers are tobacco and betel nut. Caniff and Harvey (1981) proved that areca nut extract can act as a potent stimulator of collagen synthesis in human fibroblast culture. Meijji et al (1982) showed that the tannins present in areca nut reduced the degradation of collagen by collagenase. Chewing of pan which consists of the ripe betel leaf coated with crude lime, sprinkled with powdered acacia catechu, containing small pieces of areca catechu nut, few dried leaves of anethum graveolens with or without tobacco. Some people chew pieces of areca catechu alone or scented supari, others chew crude tobacco or tobacco mixed with lime which is usually placed in the vestibule of the mouth for slow absorption (DeSa 1957). The habit of chewing of Pan Masalas are of recent origin. All varieties of Pan Masalas contain nearly all the constituent of betel quid except betel leaves. However, Varghesse et al (1986) reported that arecoline plays no significant role in the causation of human submucous fibrosis as there were six patient studied by them who had never taken Pan, betel or tobacco any time in their life.
Dietatic Habit

Since the disease occurs predominantly among Indians and peoples of Indian origin, a possible cause has been suspected in their common diet. Spices like pepper and chillies (Capsicum annum and Capsicum frutescens) being an essential ingredient in Indian diet, are universally used in all parts of India to season food. Support for this theory, that chillies also may be a causative factor, is found in the occurrence of submucous fibrosis among Indians living outside India but maintaining Indian dietary habits. An allergic reaction has been suggested as the possible cause of oral submucous fibrosis (OSMF) (Sirsat and Khanolkar, 1962; Pindborg et al., 1968), the possible allergen which has been suspected, common in the Indian diet, is chillies (Hammer et al., 1974).

Collagen Disease

Clinical picture of stiffness and immobility of oral mucosa and histological changes in connective tissue suggested a collagen disease (DeSa, 1957; Meas and Madan, 1968).

According to Rao, A.B.N. (1961) it will be more logical to group this condition with localised forms of collagen diseases such as Peyronie's disease.
Dupuytren's contracture, Keloids, idiopathic retro-peritoneal fibrosis (Raper, 1960) and idiopathic mediastinal fibrosis (Barrett, 1938).

**Genetics:**

Genetic factors might play some role in genesis of oral submucous fibrosis (Hammer et al, 1971).

**Oral Infections:**

The role of oral infections as a factor for causing oral submucous fibrosis has been emphasised (DeSa, 1957).

**Vitamin Deficiency:**

Wahi et al (1960) had suggested the Vitamin A and B deficiency associated with tobacco chewing may be the possible cause.

**Symptomatology:**

Earliest symptoms are burning sensation of the oral mucosa, inability to eat spicy food, stomatitis, dryness of the mouth or excessive salivation, vesicle formation and ulcerations. Later stiffness of certain areas of the oral mucosa result in inability to open the mouth completely, to protrude the tongue, to whistle
or to blow out a candle, trismus, referred pain in the ears, deafness or nasal voice may be observed in some cases.

Clinically the disease may be divided into three stages, in which the patient present themselves for treatment: Stage I - Stomatitis or Vesiculation; Stage II - Fibrosis; Stage III - Sequelae (DeSa 1957).

**Oral submucous fibrosis as a precancerous condition**

The possible precancerous nature of submucous fibrosis was first mentioned by Paymaster (1956) who described the development of slow growing squamous cell carcinoma in a third decade of the one third patients with submucous fibrosis. Sirsat and Khanolkar (1963) has reported malignancy in four out of 85 cases (4.7%). Pindborg (1965) demonstrated that Indian patients with submucous fibrosis have a higher incidence of leukoplakia and of carcinoma than those without the disease. In subsequent study Pindborg (1965) has himself reported 40 cases of submucous fibrosis among 100 Indians with oral cancer. Wahi et al (1966) had found cancerous change in 3% of cases.

**Histopathological changes**

Sharan (1959), Rao (1962), Sirsat and Khanolkar (1957 and 1962), Wahi (1965) have described the histological
changes found in submucous fibrosis. Histologically most of the cases are characterised by atrophy of the epithelial layer with loss of rests pegs. Epithelial atypia is also present in a few of the cases. The underlying connective tissue shows severe hyalinization with homogenization of collagen bundles. Fibroblasts are markedly diminished and blood vessels are completely obliterated or narrowed. Some chronic inflammatory cells infiltration is also present.

**Cytological study of submucous fibrosis**

Wahi and Luthra (1966) had studied the oral scrapes of patients of oral submucous fibrosis and reported that smears from these cases showed a preponderance of superficial cells while intermediate and parabasal cells were less frequent.

In these smears they found that the anucleated squamous cell were isolated or in clusters. Frequently the cytoplasm was eosinophilic and occasionally it was intensely orangophilic. Sometimes these cells showed the presence of 4 to 10 brown to black cytoplasmic granules. A majority of the cells showed a cyanophilic cytoplasm with vacuolation and perinuclear haloes. The nuclei were round to oval with distinct nuclear membrane, prominent nucleoli and the chromatin presented a peculiar 'rarified' pattern.
III. **LICHEN PLANUS**

It literally means a cryptogenic mass like plant (algae and fungi mixed) forming patches on rocks or tree trunk.

It is generally discovered only by accident, but often the patient will complain of discomfort or soreness of oral mucosa (Shklar and McCarthy, 1961; Kramer et al, 1970). Mucosal lesions are usually multiple and often have a symmetrical distribution. They commonly take the form of minute white papules which gradually enlarge and coalesce to form either a reticular, annular or plaque pattern. A characteristic feature is the presence of slender white lines (Wickham’s Striae) radiating from the papules. The plaque form may be difficult to distinguish from leukoplakia, but in lichen planus there is usually no change in the flexibility of the affected mucosa. In some patient the lesions are atrophic, with or without erosions. Oral lesions of lichen planus may also include bullae, but these are rare (Kramer, 1978). Histologically there is hyperkeratosis or parakeratosis and thickening of the granular layer, acanthosis with intracellular edema of the spinous cells, 'saw-tooth' appearance of the rete pegs is less frequent, necrosis or liquefaction degeneration of the basal layers of cells with the appearance of a thin band of eosinophilic
agulum in the place of this basal layer and finally, infiltration of lymphocytes and only occasional plasma cells into the sub-epithelial layer of connective tissue (Shafer - A text book of oral Pathology, 1967).

Many earlier reports suggest the premalignant nature of oral lichen planus (Cawson, 1968). Carcinoma may arise in oral lichen planus but does so only rarely (Shklar and McCarthy, 1961; Kovesti and Banoczy, 1973), and there is greater risk when lichen planus is in the atrophic or erosive form (Kramer, 1976).

Silverman (1974) found average age of onset to be slightly over 50 years. In his study, 65% cases were women and majority of them had erosive type of lesions. Skin involvement was only in 20%. There was no apparent causative factor. In a study of Bhonsale (1976) amongst reverse 'dhumti' smokers of Goa, India, the incidence of Lichen Planus of the mouth was 0.2%.

According to Wahi et al (1966) the smears of the patients of Lichen Planus are characterised by abundant exfoliation of epithelial and inflammatory cells. Nucleated superficial cells predominate. Cytoplasmic vacuolation and nuclear fragmentation are prominent features. Leukocytic inclusions are seen in
some pre-cornified and cornified cells. The chromatin pattern is a predominantly finely granular. Intermediate and basal cells occur in small groups or isolated. These are markedly enlarged and show large cytoplasmic vacuoles. The nuclei are round to oval and show distinct nuclear membrane. Few basal cells show multi-nucleation (3-5 nuclei).

IV. **ERYTHROPLAKIA**

Erythroplakia is defined as a brilliant, dark red circumscribed lesions that can not be rubbed off and is not ascribable to any other definitive condition. It presents as velvety red patches that slowly spreads. The margin of such a lesion may also show whitish (leukoplakic) changes. Usually the epithelium is thinner than normal and may show typical change of carcinoma-in-situ (Shafer, 1975). Erythroplakia is less common than leukoplakia and has, on the whole, greater malignant potential. Kramer (1973) has said that erythroplakia should be regarded as carcinoma until proved otherwise.

Cytological findings in cases of melanoplakia and erythroplakia are similar to leukoplakia in cell type and chromatin pattern. No melanin pigment containing cells are seen in cases of melanoplakia (Wahi et al., 1966).
VI. PLUMMER VINSON SYNDROME

The plummer-vinson syndrome (also known as Paterson-Brown-Kelly syndrome), a form of iron deficiency anaemia was first described by plummer in 1914 and by Vinson in 1922 under the term "hysterical dysphagia". Ahlom (1936) defined it as a predisposition for the development of carcinoma in the upper alimentary tract. It is an established precancerous condition for causation of post cricoid carcinoma in females, specially in Western countries. However, its association with oral cancer also was shown by Wynder et al (1957) in Sweden.

It occurs chiefly in women in the fourth and fifth decades of life. Presenting symptoms are cracks of fissures at the corners of mouth, a lemon tinted pallor of skin, a smooth, red, painful tongue with atrophy of the filiform and later the fungiform papillae, and dysphagia. The mucous membrane of the oral cavity and oesophagus are atrophic and show loss of normal keratinization. Momto and his associates (1961) reported unusual alterations in exfoliated squamous epithelial cells of the tongue in cases of severe iron deficiency anaemia. These changes consisted of a deficiency of keratinized cells, a reduced cytoplasmic diameter of cells with a paradoxical enlargement of the nucleus, and abnormal cellular maturation characterized by a disturbed nuclear pattern, an increase in nucleoli, presence of double nuclei and hemanthemia.
VII. 

**LEUKOCYTIC NICOTINA (LEUKOCYTIC NICOTINA)**

**PALATI. NICOTINIC (NICATILIS):**

It is already established that many habits produce epithelial changes in the buccal mucosa. Sirsat et al (1974) found that tobacco taken in any form, produces a more profound degree of keratinisation. The habit of reverse smoking, prevalent in certain parts of India, produces an extensive hyperorthokeratosis often associated with epithelial atypia of the palatal mucosa (Mehta et al, 1969; Pindborg et al, 1971). Reddy (1974) in his studies of cancer of the palate among reverse smokers, found the association of stomatitis nicotina, a popular umbilicated lesion in the glandular zone of the hard palate to be premalignant.

In the early stages of stomatitis nicotina, the mucosa is reddened, but it soon becomes greyish white and may present a wrinkled appearance. Later it becomes thickened, and white umbilicated nodules with red centres appear. Histopathologically the epithelium shows acanthosis and hyperorthokeratosis and hyperparakeratosis is seen around the orifices of the ducts of the palatal mucous glands. The epithelium lining often shows squamous metaplasia. There is usually a moderate degree of chronic inflammatory infiltration in the subepithelium connective tissue and around the gland acini.
Stomatitis nicotina is often a reversible condition that is resolved when smoking is discontinued (WHO collaborating centre for oral pre-cancerous lesions, 1978).

VIII. **ORAL CANDIDOSIS**

Eyer and Nally (1971), while presenting three cases of chronic oral candidosis observed eventual malignant change in two, and opined that there is a definite propensity for malignant change in these lesions.

In the chronic infection there may be gross epithelial hyperplasia. A moderate degree of epithelial dysplasia is often seen, but there is evidence that this may regress if the candidal infection is eliminated. However, there is also some evidence to suggest that malignant changes are more likely to occur in chronic candidal leukoplakia than in non-candidal leukoplakia, the inter-relationship between candidal infection, the epithelial dysplasia and the risk of future malignancy remain uncertain. (WHO Collaborating Centre for Oral precancerous lesions, 1978).
IX. DENTAL AND ORAL INFECTIONS

Lash et al (1961) among many others, found a common association of oral sepsis with carcinoma of the tongue. However, Cade and Lee (1957) observed healthy oral mucosa associated with the same disease. Though none yet has been able to show definitely an association of dental irritation and trauma as significant factors in oral cancer, Wood (1961) considers the rising standard of oral hygiene to be a possible factor in decreasing the death rate from oral cancers in Western countries.

X. SYPHILIS

Wynder et al (1957) found that syphilis was shown to be of some importance in the development of cancer of the lip and of the anterior two-thirds of the tongue. It can not be established whether this relationship is due to syphilitic glossitis or to arsenical therapy, which most of these patients have received. At any rate, with the modern methods for control of syphilis through its early treatment with antibiotics, this factor will be less important.
MALIGNANT ORAL LESIONS:

Malignant lesions of the oral cavity originate from epithelial tissues or the mesodermal elements. Carcinomas, i.e., malignant lesions of epithelial origin is the commonest variety encountered and of these, squamous cell carcinomas are the commonest. Pathological aspects of the lesions in various sites are described below:

Carcinoma of the lip:

The incidence varies in different parts of the globe. It is more in males. Spitzer et al (1975) in a study found that, despite the effect of pipe smoking, outdoorness and age on the lip cancer in general, the occupation of fishing is an additional independent risk. Khanolkar (1959) observed a high frequency of carcinoma of the lower lip, specially in males in Bihar and adjacent areas of Uttar Pradesh, India, where the habit of keeping 'Khaini', quid of powdered tobacco and slaked lime in lower gingivalabial sulcus for many hours is common.

The lesion starts as a small warty growth, ulcer or a fissure on the mucosal surface of the lip. Ulcerative forms progress relatively rapidly and invade deeper tissues and adjacent structures early.
Lymphnode metastasis occurs relatively late and when occurs, submental and submandibular nodes are the first to be involved with subsequent extension to the upper deep cervical nodes. Histologically majority of the tumours are well differentiated.

**Carcinoma of the buccal mucosa:**

"Carcinoma of the buccal mucosa overshadows all other type of oral cancers in the South-Western Coastal regions of India" - Barash (1964). The term buccal mucosa here indicates the mucosa of the buccal aspect of the cheek. Carcinoma usually starts in the region opposite the lower third molar tooth. It may also start as a malignant transformation of the pre-existing leukoplakic patch. The tumour starts as a small nodule, enlarges to form a wartlike growth and then ulcerates. The lesions may, however, start as an ulceration. Extension to surrounding areas takes place leading to trismus, dysphagia and various other manifestations. Metastasis reach to submandibular and upper deep cervical nodes. Histological picture in majority of cases shows a well differentiated squamous cell carcinoma.

**Carcinoma of the Gum:**

Carcinoma of the gum may arise from two sources, the common epidermoid carcinoma from the mucosa and carcinoma from minor salivary glands present in the alveolus.
The carcinoma occurs generally in the pre-molar and molar regions and common site of occurrence is the lower alveolus. Cooke (1976) attributed the occurrence to chewing of betel nut with tobacco and slaked lime and the anatomical flow of saliva. Smoking is another important aetiological factor (Cady and Catlin, 1969). Males are more affected than females.

The growth may be ulcerative or papillary, with the former having more tendency to invade the underlying tissues and bone at an early stage. However, cancers from minor salivary glands, though commonly present as non-ulcerated masses frequently invade the underlying bone (Cady and Mutter, 1969). Microscopically carcinoma gingivae is practically always a well differentiated variety. Metastasis takes place early, more in cases of lower gum to submandibular nodes and then to the cervical nodes.

**Carcinoma of the floor of the mouth:**

The relatively slow growing carcinoma generally occurs in the anterior portion of the floor of the mouth away from the midline, in the region of the junction with the tongue. The tumour may present as a wartlike growth and remain superficially, may be ulcerative or even may remain in the submucosa presenting
as a fissure in the oral cavity. Lymph node metastasis occurs in most cases to submandibular and submental nodes. Histologically most of them are well differentiated.

**Carcinoma of the hard palate:**

Carcinoma of the hard palate is prevalent in certain districts of Andhra Pradesh, India, where the habit of reverse smoking of local cigars 'Chutta' is common. The tumour may be of a papillary variety or an ulcerative growth invading the under-lying bone and thus, may cause perforation of the palate. Emrath et al (1970) showed a high incidence of mucosuedemoid carcinoma occurring from the covering epithelium of the terminal portion of the ducts of the minor salivary glands. There is both mucous secreting cell proliferation and epidermoid differentiation. The poorly differentiated variety is highly malignant. Reddy et al(1974) observed a high incidence of carcinoma palate in females reverse smokers in the posterior half of the hard palates away from the midline where there is the highest concentration of glands. Lymph node metastasis occurs in 30% cases (Lucas, 1964).

**Carcinoma of the anterior two-thirds of the tongue:**

The lesion shows a higher sex incidence in male and occurs mainly in middle and old age. Chronic
irritation and syphilis, if present may play a part in its occurrence. Hyperkeratosis or leukoplakia is a precursor. The lesion may present initially as a small papilloma or a warty growth or as an ulcer with everted edges. The usual site of occurrence is lateral border of the middle third of tongue, microscopically, usually an epidermoid carcinoma showing higher grades of differentiation. Infiltration to submandibular and submental nodes is rapid, leading to fixation of the tongue. Prognosis is comparatively poor.

**Some uncommon malignant tumours of oral cavity:**

**Verrucous carcinoma:**

A slow growing carcinoma, occurs chiefly in older age group above the age of 60, and affects the buccal mucosa, gingiva, palate, tongue and tonsils. The lesion is a papillary mass composed of heaped up folds of tissue. Though characteristically indolent, local infiltration may occur up to bones. Lymph node metastasis never occurs, though there may be inflammatory enlargement of regional lymph nodes. Microscopically, it is always well differentiated with intact basement membrane making the diagnosis of carcinoma difficult. Prognosis with proper treatment is excellent.
Malignant melanoma:

Also known as melanocarcinoma, it is a rare tumour in this region. The tumour arises from melanoblasts and oral melanosis may be a precursor. The biological characteristics of the tumour, in this region, have a great tendency to infiltrate the adjacent tissue structures and a greater disposition to metastasis (Reicev and Buryak, 1970). It may progress, unnoticed, in the oral area until it reaches a considerable size (Shimada, 1976). Boman and Sirsat (1974) presenting a series of 24 cases of malignant melanoma in Indians, found a high incidence in males. The common site of affection was the alveolus and palate.

Malignant connective tissue tumours:

Malignant connective tissue tumours in the oral cavity are very rare. Various types such as fibrosarcoma, lymphosarcoma, osteogenic sarcoma, reticulum cell sarcoma, liposarcoma have all been reported.

Multicentric oral carcinoma:

Oral carcinoma may be multicentric in origin particularly in heavy smokers. This may be due to the abnormal state of the oral mucosa for a longer period of time under the influence of chronic irritation prior to the development of overt carcinoma (Slaughter
and colleagues, 1946, 1953). Oral carcinoma may also be associated with primary carcinoma elsewhere in the body. Two or more oral carcinomas or additional malignancies in the pharynx, oesophagus and other structures have been reported (Moertal et al, 1958; Sharp et al, 1961; Meyer and Shklov, 1960).

**Malignant tumours of the Oropharynx**

Malignant lesions may occur in any parts of the oropharynx and like the oral cavity, in this region also, squamous cell carcinoma is by far the commonest variety of malignancy encountered.

**Carcinoma of the soft palate and fauces**

Carcinoma of the soft palate and uvula is commoner than that of the hard palate. Posterio border is the usual site to start with. Seydel and Scholl (1974) in their study, found that the lesion occurs in male after fifth decades of life. Carcinoma highly differentiated is usually of epidermoid variety (Mjertman and Emeroth, 1970). Local spread takes place to the pterygoid fossa, hard palate etc, leading to trismus, dysphagia. Metastasis takes place to upper deep cervical nodes. There is often bilateral involvement of the nodes in central soft palate lesions.
Malignancy of the tonsils & malignancy of the base of tongue:

They are carcinoma, lymphoepithelioma and lymphosarcoma of which carcinomas are the commonest. Carcinoma of tonsil is one of the common variety of oropharyngeal malignancies. The lesion is uncommon before the age of 50 years and the incidence is higher in males. It is more prevalent in heavy smokers, heavy drinkers and those who have poor oral hygiene (Fleming et al, 1976). The lesion may be proliferative or ulcerative.

Malignancy of the base of the tongue:

Malignancies of the base of the tongue are also carcinomas, lymphoepitheliomas and lymphosarcomas, of which carcinomas are the commonest. Pathologically it is similar to malignancy in the tonsil. But, because of involvement of the tongue musculature, there is alteration of speech, the so-called 'hot potato voice' (DeWeese and Saunders, 1972). There is often bilateral involvement of upper deep cervical nodes.

Malignancy of the oropharyngeal wall:

Most of the tumours are carcinomas showing a high degree of malignancy. The growth may be proliferative or ulcerative showing low grades of differentiation. Regional lymph node metastasis is early and bilateral involvement takes place in the posterior oropharyngeal wall lesions. Overall prognosis is poor.
AETIOLOGICAL FACTORS IN THE GENESIS OF CARCINOMA OF THE ORAL CAVITY:

The etiology of oral carcinoma is as debatable and diverse as any other aspect of the condition. Various etiological factors suspected to be related to cancer of oral cavity are as follows:-

**Tobacco**:

The high incidence of oral cancer in India has been associated with tobacco chewing and/or tobacco smoking habits (Khanolkar, 1944, 1959; Sanghvi et al, 1955; Shanta and Krishnamurti, 1963; Paymasyer, 1971; Wahi, 1968; Reddy et al, 1975; Khanna et al, 1975).

The effect of smoking are partly the result of the heat generated and partly due to the chemical composition of fumes. It is fully established that tobacco products are carcinogenic. Keer (1948) states that nicotine alone does not change or cause the condition. Tars contain Benzpyrene which produces carcinoma in experimental animals. The effect on the mucosa usually occurs in a heavy smokers. If the pipe or cigarette is habitually held in one position, only the area on which the smoke chiefly impinges, may be involved (McCarthy, 1936).
Wynder and Bross (1957) have reported that the smoking chiefly of cigarette and pipes is responsible for oral cancer while cigarette smoking causes mainly lung cancer.

In the series of Wahi et al. (1958), 88 cases in a total of 750 were smokers, out of which 64 cases were associated with tobacco chewing. They are of the view that in our country smoking of cigarette and bidis is less responsible for oral cancers than the tobacco chewing. It is possible that smoking continued over a long period may contribute to the development of cancer of the lip and tongue due to combined action of heat and tobacco carcinogens. 74% of patients who chewed tobacco had cancer on the side on which they kept the quid (Chawla et al., 1969). Jassawala and Desh Pande (1971) made a retrospective study of cancer at high risk sites at Bombay Registry and found chewing and smoking of tobacco as etiological factor of oral, pharyngeal, laryngeal and oesophageal cancers. The risk of developing cancer in buccal mucosa was found to be 7.7 times higher in chewers than in non-chewers.

**Alcohol:**

Wynder and Bross (1957) reported that alcohol has a marked influence on the development of cancer of the mouth. This could be due to a direct effect of the
alcohol on the tissues or may be due to a decrease of protective saliva from the mucosa, which would tend to make it more susceptible to the effect of tobacco. A third possibility is an indirect action due to nutritional deficiencies. Alcoholics develop deficiencies of ascorbid acid, thiamine, riboflavin, and upon liver involvement, also of vitamin A (Jellinck and Jelliffe, 1940).

Cade and Lee (1957) found that heavy alcohol consumption particularly whisky to be of a significant factor among patients of carcinoma of oral cavity.

**Dental conditions and poor oral hygiene:**

Trauma and irritation due to ill fitting dentures or a sharp jagged tooth also predisposes to the development of oral cancer. Khanolkar (1944) notes that chronic irritation from a jagged tooth has no part in the causation of cancer in Bombay but Salendra (1949) considers that it is an important factor.

A poor oral hygiene is commonly met in all the cancer patients in India. There is tartar deposition over the teeth and advanced pyorrhoea usually in all cases of oral cancer (Wahi et al, 1958).
**Nutritional Deficiency:**

The frequency of oral carcinoma shows a close relation to the economic status which in turn indirectly related to quality of the food of the individuals. Most of the patients suffered from mild to severe degree of avitaminosis (Orz, 1933; Wahi, 1958).

Martin and Koop (1942) have stressed that malnutrition and vitamin B-complex deficiency with vitamin A deficiency are probably associated with oral cancer.

**Social Status:**

Carcinoma of the oral cavity is found to be more in individuals of the labour and lower middle class group (Wahi et al., 1965). This may be explained as a result of poor oral hygiene and gross oral sepsis in this class of people.

**Syphilis:**

Syphilis was shown to be some importance in the development of cancer of the lip and of the anterior two thirds of the tongue (Wynder et al., 1975).

**Geographical Distribution and Incidence:**

International Union against cancer (U.I.C.C., 1970) in its publication reported higher incidence of cancer of mouth, tongue and pharynx in India in relation to other countries (cited from Agarwal et al., 1985).
Cancer of the oral cavity is common in India, where it accounts for 40% of all male cancer admissions to the Tata Memorial Hospital, (Khanolkar, 1950).

Dr. David Branes (1980), Chief of the Oral Health Programme of W.H.O., has also indicated in a report that the incidence of mouth cancer is highest in India, being 35 to 40% as compared to only 3 to 5% in North American and European countries (cited from Agarwal et al, 1985).

A statistical survey was undertaken by Kini and Subba Rao (1937) as regards the cancer palate, which was prevalent in the women of Vishakhapetnam District of Andhra Pradesh. It is due to peculiar habit of reverse smoking of cigar (Chutta).

**SITES OF INVOLVEMENT IN ORAL CAVITY**

The cheek and other unspecified part of mouth were found to be more commonly involved (Wahi et al, 1965 from Agra, U.P. and Gangadharan, 1979 from Kanpur), followed by tongue. However, Jussawalla (1980) has reported the reverse i.e., hypopharynx to be commoner than cheek, in the Bombay Cancer Registry.
TABLE NC. II

Site wise frequency of oral cancer as reported by different observers.

<table>
<thead>
<tr>
<th>Name of Authors</th>
<th>Total cases</th>
<th>Lips %</th>
<th>Buccal mucosa %</th>
<th>Tongue %</th>
<th>Gingival %</th>
<th>Palate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahi et al, 1965 Agra (India)</td>
<td>1916</td>
<td>2.6</td>
<td>52.3</td>
<td>26.9</td>
<td>10.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Khanolkar, 1946 Bombay (India)</td>
<td>1000</td>
<td>1.7</td>
<td>16.5</td>
<td>52.2</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Khanolkar and Suryabai, 1945 Vishakhapatnam (India)</td>
<td>285</td>
<td>7.0</td>
<td>15.4</td>
<td>27.7</td>
<td>4.9</td>
<td>36.0</td>
</tr>
<tr>
<td>Somervell, 1944 Travencore (India)</td>
<td>3397</td>
<td>6.0</td>
<td>45.5</td>
<td>13.0</td>
<td>35.0</td>
<td>-</td>
</tr>
<tr>
<td>Malher, P.K. 1949 - 1952 Agra (India)</td>
<td>600</td>
<td>3.4</td>
<td>54.1</td>
<td>26.0</td>
<td>8.3</td>
<td>8.2</td>
</tr>
</tbody>
</table>

AGE:

Incidence of oral cancer was more common in persons above 50 years age (Orr, 1933; Paymaster, 1937).

SEX:

The oral cancer is more prevalent in males as compared to females, the ratio being 2:1 (Wahi et al., 1950).

In Sweden, cancer of the tongue, gum and buccal mucosa is about as frequent in women as in men, due to prevalence of Plummer-Vinson disease among Swedish women (Wynder et al., 1937).
RELIGION:

Wahi et al (1952) reported that in their series Hindus were affected 1.8 times more than Muslims.

ORAL AND GLOTTICAL TUMOURS:

(International Histological Classification of Tumours, World Health Organization).

I. TUMOURS OF SQUAMOUS EPITHELIUM

(A) BENIGN

1. Squamous cell papilloma

(B) MALIGNANT

1. Intraepithelial carcinoma (Carcinoma in situ)
2. Squamous cell carcinoma
3. Variants of squamous cell carcinoma
   (a) Verruous carcinoma
   (b) Spindle-cell carcinoma
   (c) Lymphoepithelioma

II. TUMOURS OF GLANDULAR EPITHELIUM

III. TUMOURS OF SOFT TISSUES

(A) BENIGN

1. Fibroma
2. Lipoma
3. Leiomyoma
4. Rhabdomyoma
5. Chondroma
6. Osteochondroma
7. Haemanxioma
   (a) Capillary
   (b) Cavernous
8. Benign haemangioendothelioma
9. Benign haemangiopericytoma
10. Lymphangioma
    (a) Capillary
    (b) Cavernous
    (c) Cystic
11. Neurofibroma
12. Neurilemoma (Schwannoma)

(B) MALIGNANT
1. Fibrosarcoma
2. Liposarcoma
3. Rhabdomyosarcoma
4. Leiomyosarcoma
5. Chondrosarcoma
6. Malignant haemangioendothelioma (angiosarcoma)
7. Malignant haemangiopericytoma
8. Malignant lymphangioendothelioma
   (lymphangiosarcoma)
9. Malignant schwannoma
IV. TUMOURS OF THE MELANOCYTIC SYSTEM

(A) BENIGN

Pigmented naevus

Non-pigmented naevus

(B) MALIGNANT

Malignant melanoma

V. TUMOURS OF DETERMINED OR UNDETERMINED HISTOGENESIS

(A) BENIGN

1. Myxoma

2. Granular cell tumour
   (Granular cell "Myoblastoma").

3. Congenital "Myoblastoma"

(B) MALIGNANT

1. Malignant granular cell tumour
   (Malignant (monomorphoid) granular
   cell "Myoblastoma").

2. Alveolar soft-part sarcoma
   (Malignant organoid granular cell
   "Myoblastoma").

3. Kaposi's sarcoma

VI. UNCLASSIFIED TUMOURS

VII. TUMOUR LIKE CONDITIONS

1. Verruca vulgaris

2. Papilliferous hyperplasia

3. Benign lymphoepithelial lesion

4. Maculae

5. Fibrous overgrowth
6. Congenital fibromatosis
7. Xanthogranuloma
8. Pyogenic granuloma
9. Peripheral giant cell granuloma (giant cell epulis)
10. Traumatic neuroma
11. Neurofibromatosis

Carcinoma-in-situ:

Carcinoma-in-situ (Intra-epithelial carcinoma) is characterised by an epithelium that manifests morphologic malignancy but does not demonstrate invasion of the underlying connective tissue.

It is characterised by marked cellular pleomorphism and by loss of polarity and surface stratification, with the whole thickness of the epithelium showing malignant cellular features. The basement membrane is intact. Nuclei are hyperchromatic and show wide variation in size and shape. The nucleocytoplasmic ratio is altered. Chromatin is either finely granular, or coarsely clumped and irregularly distributed. Nucleoli are enlarged and often multiple. Mitoses, often abnormal, occur in all parts of the epithelium. Subepithelial tissues commonly show chronic inflammation and increased vascularity.
CYTOPATHOLOGICAL ASPECTS OF MALIGNANCY:

A malignant cell is a modified normal cell. It varies from the normal cell in many aspects. The criteria for malignancy were studied by many authors. These criteria are present in individual cells, the cells in clusters and also there are certain indirect ways of diagnosing malignancy by cytological study.

THE CRITERIA OF MALIGNANCY IN A SINGLE CELL: They are as follows:

1. **Enlargement of nucleus**

   It is agreed that the nuclear enlargement is because of an increase in the DNA content in the malignant nucleus.

2. **Alteration of nuclear - cytoplasmic ratio (N/C ratio)**

   In normal cells, the ratio between the volumes of the nucleus and cytoplasm remains within a normal limit. However, there may be an overall increase of nucleus and cytoplasm volumes following irradiation, inflammation etc. keeping the N/C ratio within the normal limit. In malignant cells, the nuclear volume is more with proportional decrease of the volume of cytoplasm. In poorly differentiated cells, the nucleus may cover almost the whole of the cell keeping only a rim of cytoplasm around it.
3. **Hyperchromatism of the nucleus**

   The D.N.A. content in malignant cells is both increased and widely distributed. This is responsible for hyperchromatism of the nucleus with basic dyes.

4. **Coarsely granular clumping of chromatin**

   Unlike evenly distributed chromatin in the nucleus of normal cells, in cancer cells, chromatin reveals a coarsely granular or thick strandlike distribution. The space in between the chromatin clumps seem to be free of chromatin particles.

5. **Thickness and irregularity of nuclear membrane**

   This is produced by chromatin condensation at the nuclear membrane. The infoldings and irregular indentations are better visualised under electron microscope.

6. **Prominence and multiplicity of nucleoli**

   Prominence of nucleoli is because of relative increase of chromatin in the nucleoli. Also there is increase in size and number.

7. **Abnormal mitosis**

   Abnormal and frequent mitosis are indicative of malignancy although it is not usual to see it in normal cells.
8. **Multinucleation and multilobulation**

Because of abnormal mitosis, there is marked indentation and wrinkling of nuclei. However, it may be seen in benign cells like mesothelial, transitional variety etc. In such cases other characteristics of malignancy helps in contributing to the diagnosis.

9. **Variation in nuclear and cytoplasmic shape and size**

There is remarkable variation in size and shape of nuclei and cytoplasm when compared amongst one another in individual malignant cells.

**CRITERIA FOR MALIGNANCY IN A CLUSTER OF CELLS** : They are described below :-

1. **Anisokaryosis and cell clumping with pleomorphism**

Malignant cells tend to exfoliate in clumps and in these clumps, marked variation in size and shape of nuclei can be noticed as an important feature of malignancy.

2. **Irregular arrangement of cells**

There is irregular piling up of a clump of cells which is comparable to loss of polarity in the histological picture.
3. **Pair cells and inclusion cells** -

Because of incomplete division, abnormal mitosis, two malignant cells may be connected together at a portion of cytoplasm forming 'pair cells'. Because of the same phenomenon, one malignant cell may be found completely inside another malignant cell as an 'inclusion cell'.

**'DYSKARYOSIS' IN CYTOLOGICAL STUDY**

The term 'dyskaryosis' means abnormal hypertrophy of the nucleus, while the cytoplasm is well differentiated and is meant to denote abnormality in the cells in smears within benign limits. There is nuclear enlargement, hyperchromatism, irregularity of nuclear rim and multinucleation. The grades of dyskaryosis is from 'mild' to 'severe' according to the degree of nuclear abnormality.

'Mild' dyskaryosis shows slight nuclear hypertrophy, mild hyperchromatism and somewhat coarse distribution of chromatin. The cytoplasm is fairly well differentiated showing the maturity of the cells.

'Severe' dyskaryosis shows the nuclear changes closely mimicking those in the malignant cells. There are prominent nucleoli, clumping of chromatines, irregular infoldings of nuclear rim etc. Cytoplasm is not always well differentiated having an indistinct cellular border.
CELLULAR CHANGES MINICKING MALIGNANCY:

1. **Cellular changes during inflammation** -
   
   Active proliferation of cells may take place as a direct response to an injurious agent. There may be hyperchromatism, multinucleation, thickening of nuclear rim. However, there is enlargement of cytoplasm also, so that N/C ratio remains within normal limit. There may be perinuclear halo and leucocyte engulfment in the cytoplasm. In degenerated cells, nuclei vary in shape with irregular condensation of chromatin. But viable cells show round uniform nuclei.

2. **Hyperplasia and regeneration** -

   Hyperplasia indicates increase in the number of cells. The individual cells show nuclear enlargement with regular outline and normal chromatin structures. There is only mild increase in the N/C ratio.

3. **Metaplasia** -

   Metaplasia is the change in the type of adult cells in a tissue to a form which is not normal for that tissue. Metaplastic changes usually are of epithelial variety i.e. squamous metaplasia. They should be differentiated from malignant cells by the following criteria, (i) they remain in a flat sheet and contain adequate cytoplasm; (ii) chromatic arrangement in the nucleus is usually of benign nature.