7.6.4 Radio-immunoassay techniques

Radio-immunological techniques using radiolabelled antibodies can be used as in vivo imaging agents or in vitro for radio-immuno-assay and radioreceptor assay. The technique of producing clinically useful radiolabelled antibodies, the choice of radionuclide, method of conjugation, the effect of conjugation on plasma clearance and iodination techniques is reviewed by Eckelman et al. (1980).

The use of radio-labelled antibodies in the detection of head and neck squamous cell carcinoma has recently been described by Tranter et al. (1984), using iodinated anti-carcinoembryonic antigen (anti-CEA) and external radionuclide imaging technique. It is suggested that external emission scanning may find application in the detection of occult primary lesions; in the assessment of lymph node spread and metastatic sites; and in determining whether enlarged lymph nodes contain neoplasm or exhibit only reactive changes.

It has been shown by Mach et al. (1981) that anti-CEA monoclonal antibody (Mab VII 23) can localize specifically in neoplasms both by static external photoscanning and by an axial transverse tomoscintigraphic technique called single photon emission computerized tomography (SPECT) which corresponds to the application of tomographic technique used in transmission computerized axial tomography (CAT) to scintigraphic data.

7.6.5 Electron microscopic techniques

An assessment of the value of electron microscopy in the diagnosis of neoplasia in a general hospital pathology department was investigated by Fisher et al. (1985). During a three year period 235 cases were examined, of which 66 (28 per cent) presented diagnostic problems for light microscopy. In 42 (64 per cent) of the problem cases a contribution towards diagnosis was made by ultrastructural examination, which is most useful for anaplastic polygonal cell neoplasms, of some value for spindle cell neoplasms, and least helpful in the further categorization of metastatic carcinoma.

However, because of the greater technical effort involved in performing ultrastructural studies of surgical specimens and the small samples that can be examined, it is suggested by Kahn et al. (1984) that it is easier to utilize immunohistochemical, immunoperoxidase and
immunofluorescence staining in the diagnosis of anaplastic neoplasms. The combined use of immunohistochemical staining using anti-cytokeratin immunoglobulins and the ultrastructural demonstration of the epithelial features of neoplastic cells: desmosomes, tonofilaments, lumina and microvilli; should be performed to enable a more precise histopathological diagnosis of anaplastic neoplasms, thereby clarifying the histogenesis of neoplasms called "large", "small", "pleomorphic", "spindle shaped", "myxoid" or "organoid" by light microscopists (Espinoza and Azar, 1982; Kahn et al., 1984).

7.7 DIFFERENTIAL DIAGNOSIS OF ORAL SQUAMOUS CARCINOMA

Oral squamous cell carcinoma needs to be differentiated clinically and histopathologically from the following:

(1) inflammatory lesions: acute and chronic inflammation due to infection or trauma; pseudo-epitheliomatous hyperplasia; necrotizing slalometaplasia;

(2) premalignant lesions: leukoplakia, both dysplastic and non-dysplastic; erythroplakia; epithelial dysplasia; carcinoma in situ; erosive oral lichen planus; actinic keratosis;

(3) benign neoplasia: kerato-akanthoma; "inverted squamous papilloma";

(4) various types of squamous cell carcinoma: verrucous carcinoma; adenoid squamous cell carcinoma; spindle cell carcinoma; multicentric squamous cell carcinoma;

(5) metastatic carcinoma to oral soft and hard tissues; and

(6) malignant salivary gland neoplasms: adenoid cystic carcinoma and muco-epidermoid carcinoma.

7.7.1 Inflammatory lesions

Inflammatory lesions will usually resolve in 10–14 days following the institution of appropriate treatment to eradicate infection and chronic irritation. The misdiagnosis of squamous cell carcinoma of the gingiva as advanced periodontal disease can occur if histopathological investigation of suspicious persistent lesions is not performed (Torabinejad and Rick, 1980; Gallagher and Svirsky, 1984).
Oral mucosal ulcers may be due to infection, trauma or neoplasia. A neoplastic oral ulcer of advanced squamous cell carcinoma is characteristically a crateriform defect in the mucous membrane with raised, rolled margin and an indurated base and periphery. Histopathologically, the borders of such an ulcer may show hyperplasia with varying degrees of cellular atypia without keratosis. Towards the centre of the ulcer there may be a surface layer of inflammatory exudate and débris, with areas of remaining neoplastic epithelial cells arranged in sheets, strands and nests having the characteristic features of abnormal stratification, intra-epithelial keratinization, pleomorphism, hyperchromatic nuclei, increased nucleocytoplasmic ratio, etc.

According to Reade et al. (1984) chronic trauma to oral mucosa often causes an ulcer with a well defined, smooth, often raised 'white, "halo-like" border termed "peripheral keratosis". This peripheral keratosis is due to hyperplasia of the border of the traumatic ulcer, and is considered a sufficiently unique clinical sign of non-neoplastic disease. However, it is emphasized that there are no absolute clinical signs of either neoplastic or non-neoplastic oral mucosal ulcerations, and if any doubt exists definitive histopathological diagnosis is mandatory.

Pseudo-epitheliomatous hyperplasia is an histological term defined as pronounced acanthosis with extensive downgrowth of rete ridges which is occasionally mistaken for squamous cell carcinoma and kerato-acanthoma (Kissane, 1985e). Keratin "pearl" formation (dyskeratosis) may be prominent but other signs of cellular atypia are absent. Neutrophilic infiltration about the elongated rete ridges is also prominent in contrast with squamous cell carcinoma. Histological section may show isolated clumps of epithelial cells in the depth of the lesion, but these are artefactual due to the plane of section cutting across long, narrow rete processes. Other oral lesions exhibiting pseudo-epitheliomatous hyperplasia include granular cell myoblastoma and epulis fissuratum, i.e. chronic inflammatory fibrous hyperplasia. Like other inflammatory hyperplasia, pseudo-epitheliomatous hyperplasia is treated by local excision and elimination of the chronic irritating factor (Brightman, 1984c) (see Plate 16).

Necrotizing sialometaplasia is a non-neoplastic self-healing inflammatory disorder of the minor salivary glands (Lucas, 1985f; Lynch et al., 1984; Kissane, 1985c; Mitchell, 1985). It is occasionally confused
clinically and histologically with squamous cell carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. Clinically, it presents usually as a single, rarely bilateral elevated mass or crateriform ulcer, 1–2 cm in diameter involving the hard palate of adults and rarely in the mandibular retromolar region, buccal sulcus, buccal mucosa, labial mucosa, nasal fossae, nasopharynx and major salivary gland. There is a 3:1 male sex predilection with age prevalence maximum in 40–60 years group. Spontaneous healing occurs in 6–10 weeks. Pain is often the first symptom. Characteristic histological features include: coagulative lobular necrosis of the minor salivary glands; marked squamous metaplasia of mucous acini and ducts; pseudo-epitheliomatous hyperplasia of surrounding mucosa; maintenance of lobular morphology; and various amounts of granulation tissue. Mitoses and cellular atypia are not seen, but a constant feature is heavy inflammatory infiltration. The two features of necrotizing sialometaplasia, viz.: extensive pseudo-epitheliomatous hyperplasia and squamous metaplasia of salivary glands are typical of the healing process, and that the end result of a repaired lesion is a preservation of the outline of the salivary glands with replacement of the normal glandular tissues by fibrous connective tissue and squamous metaplastic acinar cells and ducts (Anneroth and Hansen, 1982). The pathogenesis of necrotizing sialometaplasia is infarction with subsequent ulceration and repair. Although the aetiology is unknown, the ischaemic necrosis is probably due to thrombosis, arteriosclerosis, arteritis or trauma. Smoking, alcohol consumption, diabetes mellitus, vascular disease and ingestion of drugs may be contributing factors (Mitchell, 1985).

7.7.2 Premalignant lesions

The definitive diagnosis of oral squamous cell carcinoma must of necessity be histopathological in order to distinguish squamous cell carcinoma from the oral premalignant lesions: dysplastic leukoplakia; erythroplakia; epithelial dysplasia; carcinoma in situ; erosive lichen planus; and actinic keratosis.
Benign neoplasia

Oral squamous cell carcinoma needs to be differentiated from kerato-acanthoma and what has been called "inverted papilloma".

Kerato-acanthoma (pseudonyms: molluscum sebaceum, molluscum pseudo-carcinomatous) is a benign epithelial neoplasm of unknown aetiology which both clinically and histologically resembles squamous cell carcinoma (Shafer et al., 1974b; Azaz and Lustman, 1974; Lucas, 1984c; Ellis, 1983; McLatchie et al., 1984; Kissane, 1985d). Takagi and Ishikawa (1982) describe two cases of kerato-acanthoma they call "idiopathic pseudo-epitheliomatous hyperplasia". Kerato-acanthoma exhibits a male predilection and a maximum age prevalence in the 50-70 years age group. The sites of predilection are mainly the epidermis, some on the labial mucocutaneous junction and, very rarely, intra-orally.

Clinically, kerato-acanthoma presents as an elevated umbilicated or crateriform lesion with a depressed central core or plug, seldom greater than 1-1.5 cm in diameter. It is a rapidly developing, exophytic, keratin-filled epithelial lesion composed of a proliferating mass of well-differentiated, keratinizing, eosinophilic, hyalinized epithelial cells with intra-epithelial micro-abscesses and a surrounding overhanging epithelial "lip". It is often painful and regional lymphadenopathy may be present. Kerato-acanthoma has an unusual clinical course beginning as a small, firm nodule developing to full size over a period of four to eight weeks, persisting as a static lesion for four to eight weeks and then undergoing spontaneous regression over the next six to eight weeks by expulsion of the keratin core with resorption of the mass, leaving little or no residual scar. Recurrence is rare.

Histologically, the lesion exhibits hyperplastic squamous epithelium growing, but not invading subjacent connective tissue, i.e. pseudo-epitheliomatous hyperplasia. There is hyperpara- or orthokeratosis with central keratin plugging and usually no epithelial dysplasia. A chronic inflammatory cell infiltrate in the corium is observed. The most characteristic feature of kerato-acanthoma is the elevation of the normal adjacent epithelium towards the central portion of the crater with an abrupt change as the hyperplastic acanthotic epithelium is reached. Perineural involvement has been noted without the corresponding evidence of malignancy (see Plate 17).
A variety of generalized eruptive kerato-acanthoma with numerous cutaneous lesions covering most of the body and involving the oral mucosa has also been described.

The pathogenesis of kerato-acanthoma is uncertain according to Lucas (1984a). It probably originates in pilosebaceous follicles of the epidermis, accounting for its rare or doubtful occurrence in oral mucosa. The status of intra-oral lesions is debatable: Svirsky et al. (1977) have suggested they may arise from ectopic sebaceous glands. Otherwise kerato-acanthoma would have to be regarded as, rarely, arising in mucosa from elements other than pilosebaceous follicles or, alternatively, mucosal lesions must be of a different nature altogether.

Excisional biopsy provides the best opportunity for diagnosis by providing a panoramic view of the entire lesion, especially of the peripheries. Treatment remains controversial with some favouring wide excision to ensure complete removal in case the lesion is a squamous carcinoma and to prevent recurrence. Long term follow up is essential as revealed by MacLatchie et al. (1984) who describe a case lost to follow up after an excision of a lesion initially diagnosed as kerato-acanthoma who died from what later proved to be invasive adenoid squamous cell carcinoma.

Takagi and Ishikawa (1982) describe "Inverted papilloma" of the oral mucosa. According to Kissane (1985) nasal and paranasal sinus papillomata are called by a "bewildering number of names". The most widely employed are "... Inverted papilloma, fungiform papilloma and cylindrical cell papilloma". These papillomata are benign, may erode bone but do not metastasize; however, five per cent of inverted papilloma or cylindrical cell papilloma show synchronous or metachronous squamous carcinoma. The carcinomata may be located in the papilloma per se or may arise at the site of a previous papilloma. These papillomata show a marked tendency to recur locally, with 30–62 per cent recurrence unless major resections are performed removing microscopic foci beyond the grossly visible lesion. Fungiform papilloma exhibits an everted or exophytic configuration microscopically, whereas inverted papilloma has invaginations or "inversions" into the underlying stroma, i.e., it is endophytic histologically. Both types are lined with various combinations of normal ciliated nasal epithelium, hyperplastic ciliated epithelium, mucous cells, squamous epithelium or intermediate epithelium. Takagi and Ishikawa (1982) suggest that inverted papilloma of the mouth is a distinct
benign lesion and warn against misdiagnosis with squamous cell carcinoma when the invaginating proliferation is confused with stromal invasion by malignant neoplastic cells.

7.7.4 Histological types of oral squamous carcinoma

The various histological types of squamous cell carcinoma, viz.: verrucous carcinoma; spindle cell carcinoma; adenoid squamous cell carcinoma need to be distinguished. A definitive diagnosis depends on the histopathological examination of representative surgical specimens. The details of the clinical and histological features of these various types of squamous cell carcinoma have been discussed previously, supra vide.

Verrucous carcinoma needs to be differentiated from diffuse verrucous lesions of the oral mucosa, viz.: exophytic papillary squamous cell carcinoma; verrucous hyperplasia and chronic hyperplastic candidiasis (candidal leukoplakia) (Shear and Pindborg, 1980; Slootweg and Müller, 1983; Eversole and Papanicolaou, 1983).

Spindle cell carcinoma is an uncommon variant of squamous cell carcinoma with a large fusiform or spindle cell component. The main problem in histopathological diagnosis is differentiating the neoplasm from fibrosarcoma and neurogenic sarcoma which exhibit the characteristic spindle shaped cells normally associated with mesodermal origin. Ultrastructural studies have proved contradictory. However, immunohistochemical techniques using monoclonal antibodies may prove to be useful in the diagnosis of spindle cell carcinoma and anaplastic neoplasia (Baumal et al., 1984) and from atypical fibroxanthoma (Kuwano et al., 1985).

Adenoid squamous cell carcinoma can be identified histologically as a distinct variant of squamous cell carcinoma. It is characterized by dysplastic squamous epithelium with lateral or deep extensions as solid and tubular ductal structures. The ductal structures are lined by cuboidal cells, and acantholytic and dyskeratotic epithelial cells are commonly found intra-luminally (Takagi et al., 1977; Tomich and Hutton, 1972). Differentiation from kerato-acanthoma can be a problem (McLatchie et al., 1984).

Multiple primary malignant neoplasms, i.e. multicentric primaries; multiple primaries of different tissues or viscera; multiple primaries of
multicentric origin plus lesions of a different tissue need to be differentiated from each other (Moertel, 1977).

7.7.5 Metastases to oral tissues

Intra-osseous carcinomata mainly due to invasion by squamous cell carcinoma need to be differentiated from metastases from distant sites and from primary intra-osseous carcinoma (McGowan, 1980; Elzay, 1982; Lucas, 1984d; Lukinmaa et al., 1985). Primary intra-osseous carcinomata arise from odontogenic cysts or vestigial odontogenic or embryonic branchial arch epithelium.

Metastatic carcinoma to oral soft tissue is rare. It may arise from primary sites in the lung, kidney, liver and less commonly from thyroid gland, trachea, skin, lymphatics, breast, pancreas, testis and uterus. Many metastases to gingivae, tongue and lip remain occult, hence the necessity to always consider metaplastic carcinoma in a differential diagnosis of oral soft tissue neoplasia (Dreizen et al., 1980; Lucas, 1984d).

Metastatic carcinoma to the jaws from primary carcinomata in the breast, lung and kidney and to a less extent from the stomach, colon, rectum, etc., usually radiographically as osteolytic lesions. Pain, labial paraesthesia, swelling of the jaws, loosening of teeth and pathological jaw fracture are common signs and symptoms (Shafer et al., 1974g; Lucas, 1984d). The clinical significance of metastatic neoplasms to the jaws lies in the fact that their detection may herald the presence of an occult primary neoplasm, or may be the first evidence of dissemination of a known neoplasm from its primary site.

7.7.6 Malignant salivary gland neoplasms

Adenoid cystic carcinoma and muco-epidermoid carcinoma of the accessory salivary glands can present clinically as painful, ulcerated intra-oral lesions, e.g.: (1) adenoid cystic carcinoma of the minor salivary glands of the palate, tongue, floor of mouth and occasionally labial mucosa and peritonsillar region; and (2) muco-epidermoid carcinoma of the palate, tongue, floor of mouth, gingiva, labial mucosa and buccal mucosa. Both types occasionally appear as intra-osseous lesions of the mandible. A detailed, concise review of both these malignant salivary gland neoplasms
is presented by Lucas (1984e). Both types need to be differentiated from squamous cell carcinoma occurring in the above locations.

7.8 EVALUATION OF HISTOPATHOLOGICALLY PROVEN SQUAMOUS CELL CARCINOMA

Once the diagnosis of oral squamous cell carcinoma is established by biopsy, a comprehensive evaluation of the patient is indicated to assure that appropriate and adequate therapeutic measures are applied. A medical risk assessment is performed which evaluates any special risks posed by the patient's compromised medical status to the proposed anaesthetic, diagnostic and surgical procedures (Brightman, 1984e). The patient is hospitalized and a complete history and physical examination is performed (Rose and Kaye, 1983a). Routine laboratory and radiographic examinations are performed (Brightman, 1984a; Kruger, 1984; Larheim et al., 1984).

New radiographic techniques are also used, e.g.: direct radiographic magnification (Clark et al., 1982); xeroradiography (Gratt et al., 1977; Jeromin et al., 1980; Gratt et al., 1980); and computed tomography (Schaefer et al., 1982; Larsson et al., 1982; Muraki et al., 1983; Harnsberger et al., 1983; Schaefer et al., 1984; Friedman et al., 1984; Mancuso, 1984; Byrd et al., 1984; Curtin et al., 1985; Husband, 1985). Computer soft-ware that manipulates the basic computed tomography (CT) data into a three dimensional surface format resembling photographs of the patient or specimen skull have been developed by Marsh and Vannier (1983) and Marsh et al. (1984).

Radionuclide scanning is useful in determining primary or metastatic neoplasms in bone, liver and spleen. Facial scintigraphy (Bergstedt et al., 1981; Weisman and Kimmelman, 1982) is useful in the assessment of mandibular invasion by oral squamous cell carcinoma.

The most important diagnostic procedure performed on all patients with head and neck malignant neoplasia is panendoscopy, which includes: laryngoscopy; tracheobronchoscopy; bronchoscopy; oesophagoscopy; and mediastinoscopy (Brightman, 1984f). Indirect or direct mirror examination or fibre-optic examination of the nasopharynx are also important.

In order to develop a co-ordinated, comprehensive, orderly treatment sequence for the individual patient, consultations with all medical specialists and supportive personnel are important (Brightman, 1984f).
These should include consultations with: (1) major group responsible for curative treatment, *i.e.*: surgeon, radiologist, medical oncologist, pathologist; and (2) minor supportive group responsible for rehabilitation of the patient, *i.e.*: dental surgeon, maxillofacial prosthodontist, general medical practitioner, dietician, speech therapist, psychiatrist, social worker, clergyman and family members. The "team approach" in the management of oral cancer has been advocated by Rapidis *et al.* (1980), *inter alios*, and is practised successfully especially in the United States of America and Europe, where the "tumour board" evaluates the accumulated data and formulates recommendations as to the appropriate patient management.
CHAPTER 8
CONCLUSION

8.1 Oral premalignancy
8.2 Pathology of neoplasia
8.3 Clinical features of oral squamous carcinoma
8.4 Aetiology of oral squamous cell carcinoma
8.5 Pathology of oral squamous cell carcinoma
8.6 Immunological aspects of oral squamous cell carcinoma
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CHAPTER 8
CONCLUSION

A review of the salient points to emerge from this clinicopathological treatise on oral squamous cell carcinoma is considered appropriate. What do we really know about oral carcinogenesis in general and oral squamous cell carcinoma in particular?

8.1 ORAL PREMALIGNANCY

The literature on oral premalignancy is full of ambiguities, uncertainties and conjecture. The underlying problem is a lack of consensus on nomenclature, with many definitions and misconceptions prevailing.

A premalignant lesion is simply defined as a lesion that may become cancerous or malignant. Oral premalignant or precancerous lesions consist of dysplastic leukoplakia; erythroplakia; carcinoma in situ; and erosive oral lichen planus.

Oral precancerous conditions are defined as clinical states or disease entities associated with a significantly increased risk of cancer. They consist of oral submucous fibrosis; tertiary syphilitic glossitis; sideropenic dysphagia (Paterson-Kelly, Plummer-Vinson syndrome); dyserkeratosis congenita; xeroderma pigmentosum; chronic oral candidiasis; and chronic discoid lupus erythematosus.

A study of oral premalignant lesions and conditions is important in the overall management of oral malignant neoplasia. However, deficits exist in our knowledge of aetiology; statistical relations between premalignant lesions and squamous cell carcinoma; identification of such lesions; and assessment of prognosis. Most of the information on oral premalignant lesions relates to leukoplakia oris, resulting in an overemphasis of leukoplakia over other more potentially serious premalignant lesions, e.g. erythroplakia and carcinoma in situ (Mashberg and Garfinkel, 1978).

At present there exists little information about the nature of the sequence of events of carcinogenesis and no evidence that detectable premalignant change is common. Squamous cell carcinoma is hypothesized
to develop from precancerous lesions or from epithelium *de novo* (MacDonald, 1975).

Premalignant change can only be diagnosed histologically by the recognition of cellular atypia and epithelial dysplasia. However, there exists two inherent problems, viz.: (1) uncertainty as to whether the most informative area (area chiefly at risk) has been chosen for biopsy; and (2) the subjective nature of the evaluation of the cellular changes and the virtual impossibility, under routine conditions, of quantifying the abnormalities regarded as significant in order to reach a useful prognosis (Cawson, 1975).

Epithelial dysplasia in oral premalignant lesions is an histological sign of impending neoplasia. Although criteria for the recognition of these individual dysplastic features have been described in detail, the final assessment is essentially subjective. Attempts to record these features more precisely and to assess their relative importance include multifactorial analyses using (1) a grading system based on photographic standards; and (2) statistical cluster and discriminant (canonical variate) analyses (Smith and Pindborg, 1969; Kramer *et al.*, 1970a, b).

Other methods do exist for more precise objective measurements of individual features but none are currently of practical value in diagnosis and prognosis, e.g. immunological, biochemical, histochemical, ultrastructural and stereological (cell kinetic) studies.

The relationship between epithelial dysplasia, carcinoma *in situ* and squamous cell carcinoma remains controversial. Cawson (1969) warns that it should not be assumed that leukoplakia oris, epithelial dysplasia and carcinoma *in situ* are inevitable, or even usual, preliminary stages of squamous cell carcinoma.

8.2 PATHOLOGY OF NEOPLASIA

The precise intracellular molecular event(s) that bring about the neoplastic transformation remains unknown. The phenotype of the neoplastic cell, however, exhibits the following salient features (Iype *et al.*, 1980): (a) altered growth properties; (2) morphological changes which may be subtle and deceptively absent; (3) karyotypic changes; (4) antigenic changes; (5) metabolic changes; and (6) cell surface and membrane changes.
There exist three categories of carcinogenic agents (Robbins et al., 1984e): (1) chemical carcinogens; (2) radiant energy; and (3) oncogenic viruses (oncoviruses).

Chemical carcinogenesis is a dynamic process involving sequential generations of cells over a variable span of time, depending mainly on the cell type, species, reactivity of the carcinogen or its metabolites and especially on dosage (Taussig, 1984b). The effects of chemical carcinogens are irreversible and there is no measurable threshold dose below which exposure has no effect.

There are two types of radiant energy (Storer, 1982; Upton, 1982): (1) ultraviolet actinic (solar) electromagnetic radiations; and (2) ionizing radiation: either electromagnetic or particulate (alpha, beta particles, nucleons). Several theories on the mechanism of radiation carcinogenesis have been proposed (Robbins et al., 1984e), viz.: (1) direct ionization of critical cellular macromolecules including a somatic mutation; (2) "indirect" theory whereby radiation first interacts with water or molecular oxygen to produce free radicals that mediate damage to DNA inducing a somatic mutation; (3) activation of latent oncogenic viruses (in certain forms of murine neoplasia); and (4) radiation-induced neoplastic transformation being the result of cell-killing followed by regenerative replication.

There currently exists no conclusive evidence of the viral aetiology of any type of human neoplasia, even though several viruses have been implicated, viz.: *Herpesvirus hominis* type 1 and 2; Epstein-Barr virus; hepatitis B virus; and molluscum contagiosum virus.

Investigations regarding the molecular biology of neoplasia have shown that aspects of the malignant character of human neoplasms are governed by the "activation" and/or the inappropriate expression of certain cellular genes resembling, but not identical to, retroviral transforming genes called oncogenes (c-onc genes) (Buick and Pollak, 1984). The relationship of cellular oncogenes to carcinogenesis is attributed to point mutations in the c-onc gene sequence creating an abnormal gene product or to a loss of regulation of transcription arising through processes such as gene amplification or translocation to a transcriptionally active area of a chromosome. However, the precise mechanism for the creation of activated oncogenes in spontaneously arising neoplasms remains obscure.
Despite the optimism that hyperactivation or mutation of proto-oncogenes may result in neoplasia, no well substantiated evidence corroborates this hypothesis for human neoplasia. No convincing evidence exists that such genes relate to the initiation or promotion events for virus-negative neoplasia. Furthermore, no statistically significant evidence exists for the qualitative changes, viz.: deletions, point mutations, recombinations, transposons or other transposable elements, or other translocated elements that alter the functions of c-onc genes in "real" human malignant neoplasia (Busch, 1984).

Cellular mechanisms of neoplasia include (Taussig, 1984a): (1) the aberrant differentiation hypothesis; (2) mutation hypothesis; (3) acquisition of viral information; (4) cellular oncogene hypothesis; (5) stem cell model; and (6) gene transcription hypothesis. The cellular oncogene hypothesis is a unifying theory of neoplasia. Its basic tenet is that neoplasia results from the activation of, or mutation in, a cellular gene responsible for normal growth control. When activated or altered the cellular gene becomes an oncogene or transforming gene that directs the neoplastic change.

Despite all the advances in the elucidation of cellular and molecular mechanisms of carcinogenesis, human neoplasia remains a complex problem. Human malignant neoplasms are primary, complex clonal aggregates with both morphological and biochemical heterogeneity that is manifested as they grow and frequently more so as they metastasize (Busch, 1984). Carcinogenesis is an aberrant developmental process which appears to begin as a rapid and irreversible alteration in isolated cells or cell populations. However, the subsequent changes in the initiated cells which culminate in neoplasia are not inevitable but many depend on other carcinogenic or co-carcinogenic environmental factors. In terms of the present concepts of cellular mechanisms of carcinogenesis little is known about the precise aetiology of human oral neoplasia.

8.3 CLINICAL FEATURES OF ORAL SQUAMOUS CARCINOMA

Oral squamous cell carcinoma and its histological variants, viz.: verrucous carcinoma; spindle cell carcinoma; and adenoid squamous cell carcinoma account for 90 per cent of all oral malignant neoplasms (Lucas, 1984).
Squamous cell carcinoma of the oral and soft tissues is usually well-differentiated and readily recognizable histologically. It can affect the labial vermillion, labial mucosa, buccal mucosa, gingivae, floor of mouth, soft palate, hard palate and tongue.

Verrucous carcinoma accounts for 5 per cent of oral squamous cell carcinoma (McCoy and Waldron, 1981; Slootweg and Müller, 1983). It is a locally invasive, late or non-metastasizing carcinoma. Sites of predilection are buccal mucosa, alveolar mucosa or gingiva. It is a slow-growing lesion that becomes a small, verrucous mass which then rapidly enlarges and becomes an indolent, fungating sessile tumour.

Spindle cell carcinoma is an uncommon histological variant of squamous cell carcinoma (Someren et al., 1976; Ellis and Corio, 1980). Sites of predilection are inferior labia oris; tongue, gingivae or alveolar mucosa. It is characterized by a polypoid, exophytic neoplasm with a short, broad peduncle, although sessile, nodular or endophytic neoplasms do occur. It has a firm, rubbery consistency without central necrosis and it exhibits extensive invasion of contiguous structures.

Adenoid squamous cell carcinoma is a rare variant of squamous cell carcinoma (Jacoway et al., 1971; Tomich and Hutton, 1972). Sites of predilection are labial vermillion, tongue, gingivae and floor of mouth. Labial lesions may be ulcerated, hyperkeratotic, "rough" or granular, or slightly elevated or nodular and are associated with areas of actinic keratosis.

Multiple primary carcinomata in contiguous epithelial surfaces have been observed in the lips, oral cavity, pharynx, larynx and oesophagus.

Intra-osseous carcinomata of the jaws are (1) mainly due to invasion from squamous cell carcinomata of adjacent structures, viz.: gingivae, tongue or floor of mouth; (2) less often represent metastatic deposits from distant anatomical sites: mammae; thyroid gland; and kidney; and (3) rarely primary carcinomata arising from odontogenic cysts or cell rests of odontogenic epithelium or vestigial embryonic epithelium from fusion sites of embryonic processes (Lucas, 1984d).

8.4 AETIOLOGY OF ORAL SQUAMOUS CELL CARCINOMA

The aetiology of oral neoplasia is unknown. Epidemiological studies, both prospective and retrospective, indicate certain "risk factors" implicated in the aetiology of oral squamous cell carcinoma. These "risk
factors" include: tobacco usage in its various forms (cigarettes, cigars, pipes, chewing tobacco, "snuff dipping"); alcoholic beverages; syphilis; iron deficiency (especially sideropenic dysphagia); chronic hyperplastic candidiasis; Herpesvirus hominis type 1; ultraviolet and ionizing irradiation. All these factors exhibit an interrelationship with at least one other factor (Binnie et al., 1983). Oral neoplasia is a multifactorial disease produced by both extrinsic and intrinsic factors acting together, some synergistically. Many of these factors may act as primary carcinogens or as co-carcinogens in the promotion of carcinogenesis following initiation.

There is ample epidemiological evidence to support the premise that tobacco consumption is a dose/time related entity in the aetiology of intra-oral squamous cell carcinoma (Binnie et al., 1983). Cultural differences in the use of tobacco products has led to variations in geographic and anatomical incidences of oral and pharyngeal cancers, in accordance with the dose-response principle (Decker and Goldstein, 1982). The indigenous tobacco smoking and chewing habits of India are seen to be primarily responsible for the high incidence of neoplasia of the upper alimentary and respiratory tracts, which account for more than half of the malignant neoplasms in males and a quarter in females (Sanghvi, 1981). Synergism between heavy tobacco consumption, heavy alcohol consumption and poor dentition has been reported (Graham et al., 1977).

Experimental evidence exists supporting the idea that tobacco consumption represents an important aetiological factor in oral carcinogenesis (McCoy et al., 1980; Trushin et al., 1985). N-nitrosopyrrolidine is found in mainstream and sidestream tobacco smoke. N'-nitrosonornicotine is the major tobacco-specific carcinogen occurring in tobacco and tobacco smoke. Hepatic microsomal alpha-hydroxylation of both these chemicals results in the formation of ultimate carcinogens. Chronic ethanol consumption increases the rates of alpha-hydroxylation suggesting an influence on the organospecificity of N'-nitrosonornicotine altering its carcinogenic potency.

The activation of polycyclic aromatic hydrocarbons to electrophilis or ultimate carcinogens in cells is mediated by a component enzyme system of microsomal mixed-function oxidase complex, referred to as aryl hydrocarbon hydroxylase (AHH) which hydroxylates polycyclic aromatic hydrocarbons to epoxides. These microsomal metabolites form covalent bonds with DNA, RNA and proteins, thereby inducing mutations (Trell et
The association of AHH activity and polycyclic aromatic hydrocarbon–induced neoplasia is widely debated and most laboratory studies have been inconclusive or contradictory.

The role of alcohol consumption in the etiology of oral neoplasia is confused, basically because of the difficulty in isolating heavy alcohol consumption from tobacco smoking (Mashberg et al., 1981; Binnie et al., 1983). Ethanol per se is not carcinogenic; however, carcinogenic contaminants or congeners present in alcoholic beverages may be of significance. A decrease in the ability of alcoholic liver to detoxify potential carcinogens and nutritional deficiencies further potentiate the systemic aspects of alcohol in the etiology of oral squamous cell carcinoma (McCoy, 1978).

Traditionally ulcer or chronic interstitial glossitis of tertiary syphilis has been associated with an increased risk of developing oral squamous cell carcinoma (Sellars, 1979; Binnie et al., 1983). More recent studies have revealed a reduced correlation between syphilis and oral squamous cell carcinoma, attributed to improved chemotherapy and the discontinuation of arsenic therapy (Decker and Goldstein, 1982). However, an expected commensurate decline in the incidence of lingual squamous cell carcinoma, if syphilis were a major risk factor, has not occurred and evidence incriminating arsenic as a cause has not emerged. It is not known whether this chronic specific infection is primarily involved in oral malignant neoplasia or whether those individuals exposed to syphilis are also more susceptible to oral carcinoma through socio–economic and behavioural factors.

At present, an epidemiological relationship exists between chronic sideropenic anaemia and oral and post–cricoid carcinoma in Swedish women. However, no causal relationship has been demonstrated (Larsson et al., 1975; Binnie et al., 1983).

Chronic hyperplastic candidiasis (candidal leukoplakia) is generally accepted as being a premalignant condition of the oral mucosa (Cawson and Binnie, 1980).

Anecdotal reports implicate Herpesvirus hominis in oral carcinoma, particularly of the lip (Hollinshead and Tarro, 1973; Tarro and Sabin, 1973; Shillitoe et al., 1981; Eglin et al., 1983). However, there is little, if any, epidemiological support for such an association between herpes labialis and oral squamous cell carcinoma (Scully and Ward–Booth, 1984).
A large body of epidemiological evidence suggests an association between labial vermilion squamous cell carcinoma and prolonged, intense exposure to actinic irradiation. All forms of tobacco usage, not just chronic chemical and thermo-mechanical irritation of pipe smoking increase the risk of labial vermilion squamous carcinoma (Decker and Goldstein, 1982). Statistical correlation of residence, nativity, outdoor occupation and age are stronger overall than that for tobacco (smoked or unsmoked) and may be more decisive than the use of tobacco in the occurrence of labial carcinoma (Keller, 1970).

Miscellaneous risk factors of oral carcinogenesis include: socio-economic factors; diet and nutrition. A statistically significant inverse relationship exists between oral cancer mortality and socio-economic status: a measure of income, education and occupation (Blot and Fraumeni, 1977; Preston-Martin et al., 1982). Occupational groups at risk of developing oral carcinoma include males in the leather and leather products, paper and chemical industries; fishing; farming; and electronics industry; and females in the apparel and textile manufacturing industries. The importance of dietary and nutritional factors in the aetiology of oral squamous cell carcinoma is difficult to determine. No significant data exist supporting the speculation that nutritional conditions, including deficiencies, predispose the individual to oral squamous cell carcinoma (Graham et al., 1977; Smith, 1979).

8.5 PATHOLOGY OF ORAL SQUAMOUS CELL CARCINOMA

The role of histopathology in the diagnosis and prognosis of oral squamous cell carcinoma is of paramount importance (Johnson, 1976; 1977). The majority of oral squamous cell carcinomata are readily diagnosable by well established, logical, histopathological criteria on routine microscopic preparations. At a cellular level squamous cell carcinoma shows disturbances in the homeostatic mechanisms controlling cell division, maturation and aggregation, as well as host response and epithelial-mesenchymal interactions.

Oral squamous cell carcinoma exhibits considerable variation in histopathological features, varying from well-differentiated through to poorly-differentiated and anaplastic carcinomata. Well-differentiated carcinoma consists of sheets and nests of large neoplastic cells with large, hyperchromatic nuclei, mitoses (usually atypical), dyskeratosis
(keratin "pearls") and vagarious (erratic) pattern of invasion. Moderately well-differentiated carcinoma exhibit less resemblances to cell of origin. There is anisocytosis, greater number of mitoses, hyperchromatic nuclei and failure of keratinization. Poorly differentiated carcinoma bears little resemblance to cell of origin, with anaplasia, a greater lack of cohesiveness and extremely vagarious patterns. Anaplastic carcinoma is very rare, metastasizes early and extensively leading to early mortality.

The histopathological characteristics of verrucous carcinoma include (McCoy and Waldron, 1981; Bohmfalk and Zallen, 1982; Mizuno et al., 1988; Medina, 1984; Lucas, 1984a):

1. verruous, densely para- and orthokeratinized squamous epithelium;
2. sharply circumscribed deep margin;
3. bulbous, well-orientated acanthotic rete processes;
4. "pushing" broad-front advancing margin;
5. normal epithelium at edge of lesion is bent back upon itself by the continued growth of neoplastic epithelium;
6. presence of epithelial "pearls" and small cysts;
7. mitoses and cellular atypia is rare; and
8. always the presence of heavy chronic inflammatory cell infiltrate.

The histopathological characteristics of adenoid squamous cell carcinoma include (Shafer et al., 1974; Tomich and Hutton, 1972; Lucas, 1984b):

1. proliferation of dysplastic epithelium into corium with lateral and deep extensions showing characteristic solid and tubular ductal structures;
2. duct-like structures lined with a layer of cuboidal cells often containing or enclosing acantholytic or dyskeratotic cells;
3. cuboidal cells exhibit pleomorphic nuclei and dense eosinophilic cytoplasm; and
4. there is a heavy chronic inflammatory cell infiltrate in the corium which nearly always shows the basophilic degeneration typical of solar damage.

Histopathologically spindle cell carcinoma is characterized by three histomorphological patterns (Someren et al., 1976; Ellis and Corio, 1980; Lucas, 1984c):
(1) fasciculated pattern: composed of highly cellular groups of elongated bipolar cells in parallel alignment with fasciculi interwoven; elongated, elliptical and vesicular cell nuclei each containing one or more nucleoli; round cells scattered among the elongated cells;

(2) myxomatous pattern: produced by spindle and stellate cells with prominent intercellular spaces, spherical vesicular nuclei with conspicuous nucleoli; and

(3) streaming pattern: composed of moderately cellular groups of spindle cells and pleomorphic cells arranged in randomly orientated cords and sheets without any notable intercellular oedema or interweaving fasciculi.

Other features of spindle cell carcinoma include: variable mitotic activity, pleomorphism, benign and atypical multinucleated giant cells, inflammation, and infiltration of contiguous structures such as skeletal muscle, bone, salivary glands and nerves.

Ultrastructural transmission electron microscopic features of oral squamous cell carcinoma include (Seifert and Burkhardt, 1977; McKinney and Singh, 1977; Löning and Burkhardt, 1982; White and Gohari, 1985): (1) cellular abnormalities; (2) cytoplasmic organelle abnormalities; (3) abnormalities in cell maturation; (4) abnormalities of basal lamina; (5) cell membrane alterations; (6) desmosomal abnormalities; (7) atypical tonofibrils; and (8) submucosal abnormalities. Ultrastructural scanning electron microscopic features of oral squamous cell carcinoma include (Reichart and Althoff, 1979): (1) areas of desquamation and invagination; (2) neoplastic epithelial cells forming nests surrounded by fine stroma; (3) surface cells exhibiting polymorphism, varying degrees of differentiation: ortho- or parakeratinization; (4) surface sometimes composed of bizarre lamellary patterns suggesting irregular keratinization; (5) cell margins showing incomplete steps; (6) cell surface with microvilli, pits and microridges; and (7) cells showing pleomorphism.

Verrucous carcinoma exhibits the ultrastructural features of well-differentiated squamous cell carcinoma (Prieoieau et al., 1980). Ultrastructural investigations of spindle cell carcinoma have proven to be contradictory in providing evidence for the pathogenesis of spindle cell carcinoma: some support a mesenchymal pathogenesis, others an epithelial one (Someren et al., 1976; Battifora, 1976; Martin and Kahn, 1977; Harris, 1982).
Histochemical investigations of malignant neoplasia are often contradictory and difficult to interpret (Johnson et al., 1980). At present no reliable histochemical or biochemical methods exist for testing the malignant potential of human oral mucosal lesions.

Cell kinetic studies of head and neck squamous cell carcinoma in humans have produced more equivocal results than from experimental animal studies (Scruggs and Johnson, 1980; 1982).

Squamous cell carcinoma of the head and neck spreads to bone and metastatic bone, i.e. laryngeal chondroskeleton, via two routes (Carter et al., 1983; Tsao et al., 1983): (1) haematogenous metastasis; and (2) direct invasion of local bones of skull. This osseous invasion occurs principally through an indirect process: (1) activation of normal osteoclasts and resorption of bone in front of advancing neoplasm's edge followed by a decline of osteoclastic response; and (2) neoplastic cells move forward onto bone surface and take over osteoclastic process. Mechanisms of osseous invasion by squamous cell carcinoma involve osteolysis due to a release of a mixture of prostaglandins (PGE₂ and PGF₂α) and non-prostaglandin osteoclastic stimulating factors (osteolysins). These osteolysins are derived from both neoplastic and stromal elements, and are "tumour-associated" rather than "tumour-specific".

Oral squamous cell carcinoma metastasizes via (Kissane, 1985b): (1) lymphatics; and less frequently (2) bloodstream and (3) perineurally. The precise role of lymph nodes in neoplasia remains unclear: they may represent an initial barrier, filter or destructive mechanism which is eventually overcome by the intensity or duration of neoplastic cell embolization. Metastases to regional lymph nodes from oral squamous cell carcinoma show varying incidence rates according to site, size and histopathological grading of neoplasm (Shingaki et al., 1985). Also, the pattern of flow of lymph rather than the detailed anatomy of the lymphatics per se is of greater importance in the dissemination of metastases (Sharpe, 1981).

Trans-capsular or extra-capsular metastasis of squamous cell carcinoma from cervical lymph nodes is a well recognized phenomenon (Carter et al., 1985; Johnson et al., 1985). Two aspects still remain confused, viz.: the reported incidence is variable; and there is no agreement regarding morphological extent: undefined extra-capsular metastasis can cover a range of changes from microscopic breaks in lymph node capsule to gross invasion of neoplasm into local tissues. The
process whereby metastatic neoplastic cells break through the nodal capsule is unclear. Spread from neoplastic emboli initially lodged in the capsular or juxtacapsular lymphatic vessels is a likely explanation. Some investigators argue that trans-capsular metastasis is the single most significant determinant for predicting recurrent cervical neoplastic disease, but the contribution of other local factors such as the number and size of involved lymph nodes, their anatomical level or levels, and pre-operative fixation are being debated (Johnson et al., 1985). Cervical lymph node metastasis of occult primary neoplasia needs to be considered in any adult who has asymmetric enlargement of one or more cervical lymph nodes (Spiro et al., 1983).

Distant metastasis of oral squamous cell carcinoma is related to the primary neoplasm sites, clinical stage of presentation and development of infectious complications during the course of the neoplastic disease (Papac, 1984). Visceral metastases are generally uncommon and practically never occur in the early stages of neoplasia. The sites with the greatest propensity to metastasize are: the palatine tonsil; oropharynx; tongue; and floor of mouth.

The nerves commonly involved in perineural spread of squamous cell carcinoma are the trigeminal nerve followed by the facial and less commonly the greater auricular and oculomotor nerves (Carter et al., 1983; Morris and Joffe, 1983). Perineural spread has been demonstrated histologically in 36 per cent of surgical resection specimens and in 90 per cent of necropsy specimens of head and neck squamous cell carcinoma. Perineural metastasis is via the perineural spaces: not part of the organized lymphatic system. Perineural infiltration involves the concentration of neoplastic cells at the margin of the nerve showing minimal extension inwards into nerve bundle but exhibiting proximal or distal extension within the perineural spaces up to two centimetres. The infiltrated nerve trunks exhibit minor degenerative changes with varying degrees of myelin and axonal degeneration, probably of anoxic origin and segmental infarction.

8.6 IMMUNOLOGICAL ASPECTS OF ORAL SQUAMOUS CELL CARCINOMA

The stromal reaction under oral epithelial dysplasia and squamous cell carcinoma involves (Scully, 1982a): (1) a predominantly mononuclear
cell infiltrate: T lymphocyte subpopulations (suppressor/cytotoxic, helper/inducer subtypes), macrophages and Langerhans' cells; and (2) the presence of Russell bodies, basal lamina defects and collagen fibre degeneration. A positive correlation exists between cellular stromal reaction and differentiation of the carcinoma, e.g. verrucous carcinoma has heavier infiltration (Johnson, 1976; Seifert and Burkhardt, 1977). It is postulated that the T lymphocyte subpopulations inhibit the development and dissemination of neoplastic cells and that this T cell infiltration correlates with the clinical course or prognosis of oral squamous cell carcinoma (Löning et al., 1983; Hiratsuka et al., 1984a, b). Langerhans' cells appear to play some unknown immunological role. Multinucleated giant cells (macrophage polykaryons) exhibiting avid phagocytic activity have also been demonstrated in oral squamous cell carcinoma (Burkhardt et al., 1976).

Regional lymph nodes can be classified into four morphological and immunological patterns (Noone et al., 1974; Jansa and Pastrnak, 1980; Ring et al., 1985):

1. lymphocyte predominance or sinus histiocytosis: reflects the active response of the thymus–dependent (T) lymphocytes linked to cellular immunity;
2. germinal centre predominance: indicates an active response in the thymus–dependent germinal centres related to humoral immunity;
3. unstimulated: reflecting no discernible response; and
4. lymphocyte depletion: referring to a lymph node with a paucity of lymphocytes.

A statistically significant prognostic value of regional lymph node patterns of the immune response has been demonstrated: lymphocyte predominance or sinus histiocytosis pattern has a better prognosis than either germinal centre predominance or unstimulated patterns. These correlations are independent of the clinical stage and metastatic nodal status.

Immunological changes in head and neck malignant neoplasms include (Scully, 1982a): (1) cell-mediated immunity: impairment of delayed hypersensitivity reactions; reduced T lymphocyte responses to mitogens and some antigens; immune complexes or suppressor cells may be implicated; (2) humoral immunity: increases in serum glycoproteins; serum carcino-embryonic antigen; serum beta-2–microglobulin; and loss of blood
group iso-antigens A and H from neoplastic cells; and (3) other humoral factors: increase in serum IgA and IgE.

The effects of specific antineoplastic responses, viz. natural killer (NK) cells; cytotoxic T lymphocytes; activated macrophages; and immunoglobulins, are most relevant in the immunological control of neoplasia by the host. Interleukin-2: a lymphokine, can generate T lymphocytes and other accessory cells cytotoxic for neoplastic cells, thereby potentiating the immune regression of solid head and neck neoplasia.

Natural killer (NK) cells are an heterogeneous population of effector cells with the capacity to spontaneously lyse target cells of widely different tissue provenance in a genetically unrestricted manner. NK cells are widely implicated in immunosurveillance against neoplastic and virus-infected cells, in homeostasis of haemopoietic differentiation and regulation of immune function (Bishop et al., 1984; Saljo et al., 1984; Kimber and Moore, 1985). NK cell-mediated cytolysis is subject to various regulatory influences, viz.: (1) potentiating effects by interferon (IFN-alpha, beta, gamma) and interleukin-2; and (2) negative regulation by certain prostaglandins (PGE1, PGE2, PGD2) and cell types including macrophages, granulocytes, thymocytes and subsets of peripheral blood lymphocytes.

A marked reduction in the random migration and chemotaxis of monocytes occurs in squamous cell carcinoma of the head and neck: the full significance of which remains unknown (Walter and Danielson, 1985).

Oral squamous cell carcinoma is associated with the expression of Herpesvirus hominis type 1 (HVH-1) antigens that stimulate IgM rather than IgG immunoglobulin response. The data is considered consistent with a role for both Herpesvirus hominis type 1 and tobacco smoking in oral carcinogenesis (Shillitoe et al., 1982; 1983; Eglin et al., 1983; Scully and Ward-Booth, 1984).

Changes in cellular antigens associated with neoplasia have been demonstrated (Old, 1981; Hendler and Ozanne, 1984), including: the reappearance of foetal antigens (oncofoetal antigens); the appearance of new antigens ("tumour-associated transplantation antigens", TATA); the loss of some antigens such as some surface histocompatibility antigens (HLA antigens); and the increase in the number of epidermal growth factor (EGF) receptors.
8.7 DIAGNOSIS OF ORAL SQUAMOUS CELL CARCINOMA

The diagnosis of overtly symptomatic oral squamous cell carcinoma is not difficult. Readily obvious are the clinical signs, viz.: ulceration; induration; fungation; fixation; bleeding; and pain. Also present may be cervical lymphadenopathy. Great difficulty is encountered with the diagnosis of early asymptomatic oral squamous carcinoma. This can be achieved by performing the following diagnostic procedures:

1. initial evaluation of suspected lesions: medical history, physical examination, photographic and/or diagrammatic documentation, elimination of predisposing factors and re-evaluation in ten to fourteen days;

2. toluidine blue vital staining of suspected lesions;

3. oral exfoliative cytology especially of ulcerative lesions;

4. biopsy and histopathological examination for a definitive diagnosis; and

5. evaluation of histologically proven neoplasia: complete medical history, physical examination, routine radiography and laboratory tests, computed tomography, radionuclide scans, liver-spleen scans, panendoscopy and clinical staging. Consultations are obtained from all the various services that may contribute to total patient care.

The main factor in the failure to detect early, asymptomatic, easily treatable oral squamous cell carcinoma is related to the propagation of ambiguous and inaccurate criteria for the diagnosis of malignant and "potentially" malignant oral mucosal lesions (Mashberg and Garfinkel, 1978). Undue emphasis is placed on the importance of recognizing "precancerous" leukoplakia oris and symptomatic oral squamous cell carcinoma with a concomitant neglect in identification of asymptomatic oral premalignant and malignant lesions. Persistent asymptomatic erythroplakia in high risk sites of the oral mucosa is the earliest and primary sign of oral squamous cell carcinoma.

Toluidine blue O (tolonium chloride) application is an established efficacious diagnostic adjunct in the detection of asymptomatic oral squamous cell carcinoma, both when applied topically or when used as a rinse for high risk patients (Poswillo, 1975; Mashberg, 1983; Silverman et al., 1984). Oral exfoliative cytology is also a useful diagnostic adjunct,
especially of ulcerated lesions and dysplastic leukoplakia erosiva (Blozis, 1972; Bánóczy, 1976).

New, potentially diagnostic techniques include: (1) ultrasonography; (2) immunohistochemistry; (3) monoclonal antibody techniques; (4) radio-immunological techniques using radiolabelled antibodies; and (5) electron microscopy.

Ultrasonography using high resolution real-time equipment has been shown to be clinically useful in precisely outlining neoplasm borders or detecting multiple or bilateral lesions of the head and neck including information on the anatomical nature of metastatic lymphadenopathy (Gooding, 1980; Ishikawa et al., 1983; Bruneton et al., 1984; Wittich et al., 1985). Furthermore, ultrasonography is a valuable surveillance technique allowing the evaluation of the efficacy of anti-neoplastic chemotherapy or radiotherapy, especially in those in whom radiotherapy has caused a thickening of cervical soft tissues.

The diagnostic efficiency of undifferentiated, anaplastic neoplasms by the surgical pathologist can be enhanced by the use of immunohistochemical immunofluorescence (IMF) and immunoperoxidase (IMP) techniques employing polyclonal and monoclonal antibodies (Baumal et al., 1984). Recently monoclonal antibodies have been developed against squamous cell carcinoma, including oral neoplasia (Carey et al., 1983; Debus et al., 1984; Pickering and Misra, 1984; Eskinazi et al., 1985; Woodhouse et al., 1985). Leukocyte adherence inhibition assay (LAI assay) is valuable in the diagnosis and monitoring of anti-neoplastic immunity of oral squamous cell carcinoma (Kövesi and Fekete, 1982; Prabha et al., 1984).

Radio-immunoassay using radiolabelled antibodies in the detection of head and neck squamous cell carcinoma has been described by Tranter et al. (1984). It is hypothesized that iodinated anti-carcinoembryonic antigen (anti-CEA) and external radionuclide imaging might be of use in the detection of occult primary lesions, in the assessment of lymph node spread and metastatic sites, and in determining whether enlarged lymph nodes contain neoplastic cells or exhibit only reactive changes.

Electron microscopic investigations have a limited value in the diagnosis of neoplasia because of the greater technical effort and cost involved. It is much easier to utilize immunohistochemical staining in the diagnosis of anaplastic neoplasms (Kahn et al., 1984).
In the differential diagnosis of oral squamous cell carcinoma the following lesions need to be discriminated, both clinically and histopathologically:

1. inflammatory lesions: acute and chronic inflammation due to infection or trauma; pseudo-epitheliomatous hyperplasia; necrotizing sialometaplasia;

2. premalignant lesions: leukoplakia oris; erythroplakia; epithelia dysplasia; carcinoma in situ; erosive oral lichen planus; actinic keratosis;

3. benign neoplasia: kerato-acanthoma, "inverted squamous papilloma";

4. various histological types of squamous carcinoma: verrucous carcinoma; adenoid squamous cell carcinoma; spindle cell carcinoma;

5. metastatic carcinoma to the oral soft and hard tissues; and

6. malignant salivary gland neoplasms: adenoid cystic carcinoma and muco-epidermoid carcinoma.

Once the diagnosis of oral squamous cell carcinoma is established by biopsy, a comprehensive evaluation of the patient is indicated to assure that appropriate and adequate therapeutic measures are applied. A medical risk assessment is performed by taking a complete medical history; physical examination; routine laboratory tests; routine and new radiographic examination: direct radiographic magnification, xeroradiography, and computed tomography; radionuclide scanning and panendoscopy (laryngoscopy, tracheobronchoscopy, oesophagoscropy and mediastinoscopy).
APPENDIX

TNM SYSTEM

Accurate clinical staging is essential for clinical assessment in studying prognosis and survival of patients suffering from malignant neoplasia. It is also necessary for epidemiological comparisons and evaluation of therapeutic procedures (Rich and Radden, 1984).

A variety of different clinicopathological classification systems have been proposed. These include:

1. Tumour, Node, Metastasis (TNM) system of the Union Internationale Contre le Cancer (U.I.C.C., 1968, 1974, 1978, 1982);

2. Tumour, Node, Metastasis (TNM) system of the American Joint Committee on Cancer (Manual for Staging of Cancer, 1978);

3. Site, Tumour, Nodes, Metastasis, Pathology (STNMP) system proposed by Rapidis et al. (1977); and

4. Treatment-Dependent Prognostic Index (TPI) proposed by the Deutsch-Österreich-Schweizerischer Arbeitskreis für Tumoren im Kiefer- und-Gesichtsbereich (DÖSAK), i.e. The German-Austrian-Swiss Association for Head and Neck Tumours (Platz et al., 1983, 1985).

The most commonly used classification systems are TNM system (U.I.C.C.) and TNM system (American Joint Committee on Cancer, A.J.C.) (see Table A1 and A2).

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumour (neoplasm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIS</td>
<td>Pre-invasive carcinoma (carcinoma <em>in situ</em>)</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour less than 2 cm in diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour 2-4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour greater than 4 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour infiltrating deeper structures</td>
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<table>
<thead>
<tr>
<th>N</th>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>Regional lymph nodes not palpable</td>
</tr>
<tr>
<td>N1</td>
<td>Movable homolateral nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Movable contralateral or bilateral nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed nodes</td>
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<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MO</td>
<td>No evidence of distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases present</td>
</tr>
</tbody>
</table>

Stage-grouping

- **Stage I**: T1 NO MO
- **Stage II**: T2 NO MO
- **Stage III**: T3 NO MO, Any T N1 MO
- **Stage IV**: T4 NO MO, T4 N1 MO, T4 N2,3 MO, Any T Any N M1
### TABLE A2: TNM System (A.J.C., 1978) for oral cavity

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary neoplasm</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour less than or equal to 2 cm in greatest diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour greater than 2 cm but less than or equal to 4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour greater than 4 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Massive tumour greater than 4 cm, with deep invasion involving antrum, pterygoid muscles, base of tongue or skin of neck</td>
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</tbody>
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<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No clinically positive nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Single clinically positive homolateral node less than or equal to 3 cm in diameter</td>
</tr>
<tr>
<td>N2</td>
<td>Single clinically positive homolateral node greater than 3 cm but less than or equal to 6 cm in diameter, or multiple clinically positive homolateral nodes, none greater than 6 cm in diameter</td>
</tr>
<tr>
<td>N2a</td>
<td>Single clinically positive node more than 3 cm but less than 6 cm in diameter</td>
</tr>
<tr>
<td>N2b</td>
<td>Multiple clinically positive homolateral nodes, none more than 6 cm in diameter</td>
</tr>
<tr>
<td>N3</td>
<td>Massive homolateral node(s), bilateral node(s) or contralateral node(s)</td>
</tr>
<tr>
<td>N3a</td>
<td>Clinically positive homolateral node(s), one of which is greater than 6 cm in diameter</td>
</tr>
<tr>
<td>N3b</td>
<td>Bilateral clinically positive nodes</td>
</tr>
<tr>
<td>N3c</td>
<td>Contralateral clinically positive node(s) only</td>
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</tbody>
</table>

<table>
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<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No (known) distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases present: specify site(s)</td>
</tr>
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TABLE A2 (continued)

Clinical stages:

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<th>Stage</th>
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<th>MO</th>
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</thead>
<tbody>
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<td>II</td>
<td>T2</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N2</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>MO</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
REFERENCES


PLATE 1. Leukoplakia simplex of the buccal mucosa (X 1).
PLATE 2. Moderate epithelial dysplasia, showing transition from normal epithelium on right of photomicrograph (Haematoxilin and eosin; X 100).

PLATE 3. Severe epithelial dysplasia. Note severely disturbed epithelial architecture (Haematoxilin and eosin; X 100).
PLATE 4. Oral carcinoma in situ. An excellent example of a focus of carcinoma in situ in hyperplastic epithelium (Courtesy of Prof. B.E.D. Cooke. Haematoxilin and eosin; X 100).

PLATE 5. Oral carcinoma in situ. Note the dense juxtaepithelial chronic inflammatory cell infiltrate composed mainly of lymphocytes (Courtesy of Prof. B.E.D. Cooke. Haematoxilin and eosin; X 100).
PLATE 6. Squamous cell carcinoma of the labial vermillion border (X 1).

PLATE 7. Squamous cell carcinoma of the floor of mouth manifesting as oral erythroplakia (X 1).
PLATE 8. Squamous cell carcinoma of the lateral border of the tongue (X 1).

PLATE 9. Squamous cell carcinoma of the soft and hard palate (X 1).
PLATE 10. Squamous cell carcinoma of the mandibular gingivae/alveolar mucosa (X 1).

PLATE 11. Early squamous cell carcinoma of the lateral border of the tongue (Haematoxilin and eosin; X 100).
PLATE 12. Squamous cell carcinoma of the lateral border of the tongue: a well differentiated, nodular, deeply infiltrating carcinoma (Haematoxilin and eosin; X 100).

PLATE 13. Squamous cell carcinoma of the lower alveolar ridge/lip: a moderately well differentiated, diffuse, deeply infiltrating carcinoma (Haematoxilin and eosin; X 40).
PLATE 14. Verrucous carcinoma of the maxillary alveolar process. Note the bulbous, well orientated acanthotic rete processes with a cryptic core of parakeratin invaginating the surface (Haematoxylin and eosin; X 100).

PLATE 15. Hyperorthokeratosis of the buccal mucosa. Note the hypergranulosis and elongated acanthotic rete processes (Haematoxylin and eosin; X 100).
PLATE 16. Pseudo-epitheliomatous hyperplasia. There is pronounced acanthosis, a prominent neutrophilic cell infiltration but no cellular atypia (Haematoxilin and eosin; X 100).

PLATE 17. Kerato-acanthoma of the labial vermilion. Note the presence of central keratin plugging and pseudo-epitheliomatous hyperplasia undermining hyperplastic epithelium, but absence of epithelial dysplasia (Haematoxilin and eosin; X 100).