



WHITE LESIONS
OF
THE ORAL CAVITY

A critical review of the literature.

This work is submitted in support of
the candidature of JOHN PATON B.D.S.
for the degree of Master of Dental
Surgery.

John Paton.
February, 1965.

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ACKNOWLEDGEMENTS

Having compiled this review of the literature concerning white lesions found in the oral cavity, the author would like to express his sincere thanks to Associate Professor D.A. Cameron, whose helpful comment and advice was much appreciated, to Associate Professor M. Jolly for his valued opinion and to Emeritus Professor A.J. Arnott for his kindness and helpfulness.

To the tolerance and ready help of his family, the writer also pays grateful and sincere tribute, for without their practical and moral support, this work would not have been possible.

INTRODUCTION

The purpose of this thesis is to set out and comment upon the pathology of white lesions of the oral cavity, a review of more recent concepts, always keeping in mind the fact that older ideas are not, per se, necessarily wrong and that past knowledge helps determine present understanding.

"White lesions" are herein defined as those abnormalities of the oral mucous membrane which demonstrate a creamy yellow to white to grey-white colouration over a more or less defined area, either large or small and may be single or multiple. No other limitations of definition will be used - all "types" of disease of the oral cavity could therefore come under this heading such as neoplasms, infections, traumas etc. if the above definition is adhered to. Ulcerative lesions, although sometimes showing a yellowish membrane or exudate, are not included: however, white lesions, ab origine, may progress to ulceration.

ORIGIN OF THE TERM "LEUKOPLAKIA"

In 1885, Butlin, referring to a case of smokers' patch on the tongue, reported by Sir James Paget, suggested the term "Leukoma".

Schwimmer, in 1877, first used the term "Leukoplakia". The word was compounded from the Greek "leucos", meaning white and "plakos" meaning tablet or block and for many years was used in its purest clinical sense. It has latterly come to describe a specific clinical condition and even to define a histopathologic one (Hellinger, 1963) both these conditions being subject to differences of diagnosis and interpretation.

The author feels that the term "leukoplakia" should be used simply to describe clinical white plates or patches as both an objective and subjective symptom before final diagnosis, which would take into account other signs and symptoms of differentiation; and, as such, "leukoplakia" could be, at times, used here in lieu of "white lesions". Sprague (1963) concludes that the term "leukoplakia" is in no current danger of being abandoned. This certainly seems the case and it is felt, therefore, that clarification of the use of the term is required by clinicians and pathologists, since it is so loosely used.

SECTION 1

PRELUDE TO DIAGNOSIS OF ORAL MUCOSAL LESIONS

A. ORAL MUCOUS MEMBRANE

An idea of the normal macroscopic and microscopic appearance of the oral mucosa would be as well outlined here.

The oral mucosa may be divided into areas corresponding to the anatomic configuration of the jaws and associated musculature. These areas are the gingiva, buccal mucosa, labial mucosa, tongue, hard palate and soft palate and the floor of the mouth. Immediately behind the oral cavity are the tonsillar area and the oropharynx, the mucosa of which may be involved and should be examined, in abnormalities of the mouth itself.

The mucous membrane of the buccal mucosa, labial mucosa, soft and hard palates and floor of the mouth should be light pink in colour and smooth in texture, - the hard palate only differing in this latter characteristic in the area of the rugae and also in its dissimilar foundations, i.e., bone instead of muscle. The gingival tissue appears normally light pink, the marginal tissue being smooth, the attached gingiva stippled. The mucosa in all the aforementioned regions should have a delicate "translucent" appearance, so that blood vessels are often seen through it. However, certain individuals, mainly Negroes, but Asians and dark complexioned peoples too, may have a naturally occurring oral pigmentation present mainly in the gingiva but almost anywhere in the mouth. It appears as a dappled brown "discolouration", diffusely and unevenly distributed.

The lingual mucosa covers a highly complex muscular system and must be adapted to its many functions. The dorsum of the tongue has a rough mucosa composed of large numbers of minute papillae, mainly

filiform, with large fungiform papillae scattered among them and appearing redder in colour than the pinkish-grey "overall" dorsal mucosa. The ventral mucosa is smooth and delicate, having no papillae and is a light pink.

Histologically, normal mucous membrane is of the stratified squamous variety and rests on connective tissue. The epithelium itself has no blood supply and thus relies entirely on the connective tissue for its nourishment. Between the epithelial cells and the connective tissue on which they rest, a basement membrane, so called, is described. Arranged at right angles to this membrane, and one cell in thickness, is the basal cell layer or stratum germinativum which serves as the progenitor of the remainder of the epidermis. These cells proliferate by mitotic division as they move toward the surface and further from their source of nourishment, they become flattened or squamous. These cells are joined by cytoplasmic bridges called "prickles", giving rise to the term prickle cell layer, also known as the stratum Malpighii or spinous cell layer, which is several cells in thickness. Moving further away from their source of nourishment, granules appear in the cells and we have what is known as the stratum granulosum. These granules are the precursors of the keratin-like group of proteins into which the whole cell is converted as it gradually "dies" of old age and lack of nourishment, flattens and becomes one of the dead keratinous flakes which form the horny surface called the stratum corneum.

It is therefore seen that the growth pattern of epithelium, its histology, is not just a "still" picture but is a dynamic process and that the tissue is in a constant state of activity or flux.

Zelickson (1963) using electron microscopy to examine mucous membrane, skin and keratinisation as well as other associated tissues and processes, discusses the aforementioned composition of mucosa in more detail. He defines a protective and a bonding property of the basement membrane, and a "prickle-cell" character of the cells of the basal layer (not seen at normal magnifications). He speaks of tonofilaments which are vertical to the surface of the mucous membrane in the basal area, but become parallel with the surface in the stratum corneum. They do not pass from cell to cell. Essential structures holding all epidermal cells together are the desmosomes (or "studs" as Mercer, 1961, terms them) which studs are thought to be anchors for the tonofilaments or fibrils. Nearer the surface, cells also possess less cytoplasmic organelles, indicating, he feels, decreased activity. Mercer speaks of keratohyalin granules or droplets which make their appearance in the stratum granulosum and there is contention as to whether they are precursors of the fibrous keratin of the stratum corneum. Zelickson says that both tonofilaments and a cementing substance are needed for keratinisation to take place, for the cement binds the filaments together in ever-increasing numbers as the surface is reached.

Dowsett (1963) summarised a study which he carried out to determine whether sex or age influenced the cellular pattern of the buccal mucosa, by stating that "within the age limits of this study and using the methods outlined, age or sex does not significantly influence the cellular pattern of the buccal mucosa". The ages of those studied ranged from 0-80 years including both sexes. The staining procedure employed was that of Papanicolaou and Traut.

THE TERMINOLOGY OF ORAL MUCOUS MEMBRANE HISTOPATHOLOGY

As before mentioned, the stratum corneum is composed of varying amounts of keratin, usually structureless fine layers of eosinophilic material with occasional cell nuclei present, when a condition of "parakeratosis" is said to exist, or clear spaces representing degenerated nuclei, a condition of "hyperkeratosis".

"Acanthosis" is a state of hyperplasia of the prickle-cell layer and "Pseudoepitheliomatous hyperplasia" is benign overgrowth of the epithelium resembling carcinoma.

"Spongiosis" is intercellular oedema of the prickle-cell layer and often predisposes to parakeratosis. There may be infiltration of polymorphonuclear leucocytes and lymphocytes between the prickle cells. The protoplasm bridges between the prickle cells are clearly visible.

"Intracellular Oedema" is often associated with intercellular oedema and gives rise to vacuolated cells.

"Vesicles and Bullae". The difference between these two is only one of size. They arise in two different ways, being collections of fluid between epithelial cells; the first is due to separation of cells of the prickle cell layer due to the breaking of their intercellular protoplasmic bonds "(acantholysis)", and secondly, the epithelial cells may themselves degenerate and the empty swollen cells form an open meshed reticulum, which latter condition is called "reticular degeneration".

"Hydropic Degeneration" is the replacement of nuclei of the cells of the stratum germinativum by clear spaces due to oedema and degeneration. The entire cells gradually degenerate and the

epithelium-connective tissue boundary is poorly defined.

"Dyskeratosis" is an abnormal orientation or development of epithelial cells showing many changes which will be enumerated and described later.

"Necrosis" is destruction of epithelium and its replacement by an amorphous mass of tissue, and "ulceration" is a break in the epithelial continuity due to destruction.

The fingerlike projections of epithelium which extend into the underlying connective tissue or "corium" are known as "rete pegs" and the connective tissue between two rete pegs is known as a dermal papilla.

KERATIN:

Areas of the mouth receiving little stimulation or traumatic influences are either non-keratinised or very lightly covered by keratin. Such areas would be the floor of the mouth, ventrum of the tongue and the soft palate. Generally though, the mouth mucosa presents a definite stratum corneum, with a thinner layer than skin. Stimulation of oral mucosa results in increased keratinisation.

LINGUAL MUCOUS MEMBRANE:

The tongue dorsum has a mucous membrane which is highly specialised, the surface being composed of papillae, mainly "filiform" with some "fungiform" and finally a few "circumvallate" papillae, about 8 to 12 in number, arranged in V-formation at the posterior part of the tongue, with the apex of the V at the foramen caecum. "Foliate" papillae are sometimes seen on either side, posteriorly; they are parallel folds of the mucosa.

B. THE SALIVA AND THE ORAL MUCOUS MEMBRANE

The oral mucous membrane is continually bathed in saliva, so that it must follow that the mucosal health is very much influenced by the state of the saliva, the major functions of which are "wetting", cleansing, digesting, aiding in swallowing, governing water intake by the dryness or wetness of the mouth which would indicate whether water intake were necessary, a demulcent property mentioned by Bibby (1949), anti-bacterial effects, healing of wounds and even an excretory function. A great deal of research in this field is yet to be done. Bibby concludes in his article on saliva that the diversity of the functions of the saliva is great and that our knowledge of this interesting body fluid is very incomplete. As long as the dentist has saliva to work with, he will continue to be in a position to make basic contributions to many scientific fields.

C. GLANDS OF THE ORAL MUCOUS MEMBRANE

1. The major salivary glands, the parotid, the submaxillary and sub-lingual are the main sources of saliva. They are supplemented by the secretions of many accessory salivary glands, situated in the submucosa and opening on to the mucous membrane surface. The latter glands are situated in the lips, cheeks, tongue and in the posterior half of the palate and their secretion is mostly mucous. The major salivary glands secrete a serous saliva, for the most part.

2. The Sebaceous Glands, usually a constituent of the skin, are not considered to be normal constituents of the oral mucosa, but their presence seems to be apparent in most adult oral cavities. Their function is not clear. The main oral site of occurrence is in the

cheeks and mention will be made of these "ectopic" inclusions later.

D. BASIC TYPES OF GROSS OR CLINICAL LESIONS OF ORAL MUCOSA

1. The Macule: is a circumscribed, non-raised area of altered colouration varying in size from a pinhead to several centimetres in diameter and it varies in shape from circular, to ovoid, to linear, being usually deeper in colour than the surrounding normal mucosa.

2. The Papule: is a small circumscribed, solid, elevated area varying in size from a pinhead to about $\frac{1}{2}$ centimetre. The base is usually roundish and the apex may be rounded, pointed or flat. They are sometimes grey-white in colour, while a lesion, composed of numbers of papules is described often as "white".

3. The Plaque: is an area of varying size, raised and firm and clear cut, whitish in colour, with a smooth to rough surface, which can also be fissured. Multiple papules may form a "plaque-like" lesion.

4. The Vesicle and Bulla: are circumscribed, elevated lesions composed of a surface covering, overlying and containing an accumulation of fluid. The covering can be thin or thick according to whether the lesion is intra- or sub-epithelial. The fluid may be clear or haemorrhagic. On rupture, of course, an ulcer is formed. Bullae are simply large vesicles and may be formed from the confluence of several vesicles.

5. The Pustule: is a vesicle containing pus.

6. The Ulcer: as mentioned earlier, is a defect or break in the epithelium, being either small (1 mm. or so) or quite large (several mms.). The ulcer floor is an acutely inflamed connective

tissue and may be yellowish, white or reddened. Ulcers are of almost any shape, with either flat, raised, undermined or ragged edges.

7. The Erosion: is a shallow defect in mucosa representing penetration down to, but not including, the basal cell layer. An erosion is usually red because of the loss of the major portion of the epithelium and the vascularity of the connective tissue shining through.

8. The Nodule: is a solid, elevated lesion, representing a mass of connective tissue elevating the overlying epithelium. The Tumour is similarly elevated and if benign, tends to be more regular and is relatively movable, while the malignant type tends to be fixed and irregular.

E. EXAMINATION OF THE PATIENT

The oral cavity should be examined fully and thoroughly for any manifestations of disease and to determine, as far as possible, the factors which have caused or contributed to any disease state.

There are four sections to any examination:

1. The History
2. The Clinical Examination
3. The Radiographic Examination
4. Special Laboratory Tests.

The clinical diagnosis is often tentative and is ascertained principally on the results of the "History" and "Clinical Examinations", while the "X-Ray Examination" and the "Laboratory Tests" are carried out only when needed.

1. The History should be derived through the following questions:

- (a) The personal history, name, age, sex, race, occupation and marital status.
- (b) The patient's complaint, if any, in simple language.
- (c) The history of his present condition, details of pain, duration, site, etc.
- (d) Past history, oral and dental, i.e. any previous dental or oral diseases, with treatment.
- (e) Medical history, which may give a clue as to diseases which have oral manifestations, to diseases which may themselves be caused by oral sepsis and lastly to conditions which may influence the type and extent of treatment.
- (f) Family history, whereby the existence of familial and hereditary diseases is recorded.

2. The Clinical Examination begins with a full examination of the oral cavity, teeth and gingivae. The state of hygiene should be noted and full dental information recorded. Missing teeth should be noted and the presence and the type of any prosthesis. The occlusion and temporo-mandibular joint should be examined and the submandibular, submental and cervical lymph nodes palpated.

The general "look" of the patient, the presence of a skin rash, pigmentation, ulcerations or swellings should be noted. The vermilion border of the lips and mucocutaneous junction should be inspected, looking for whitish areas mainly, although without the "wetting" of saliva, a lesion may not be "white".

When first looking over the mucosae, both sides of the mouth should be examined for comparison. Next examine the gingivo-buccal fornices and the posterior buccal gingivae. Examine the inside of the cheeks and lips, together with buccal and labial gingivae. If the patient tilts the head back and opens the mouth widely, the hard and soft palates can be checked. By gently depressing the tongue, the remainder of the soft palate and uvula can be seen.

Next, the patient should extend the tongue, when the dorsum may be examined, looking for white patches particularly, and if present, note whether their surface is smooth, pebbled, cracked and fissured; whether discrete or fused; if fused, do they present a picture which Cahn and Slaughter (1962) describe, quoting Butlin, as if the "tongue were covered with white paint that had hardened, dried and cracked?". Beware of this picture, since it may mask an underlying squamous cell cancer.

Indentations made by the pressure of the teeth along the sides of the tongue may mean oedema.

Next, grasp the tip of the tongue with a gauze and gently draw it first to one side and then to the other, giving good exposure of the lateral borders and noting the foliate papillae posteriorly, particularly the junction of the tongue to the anterior tonsillar pillar, where symptomless lesions may occur.

If the tip of the tongue is made to touch the roof of the mouth, a view of the floor of the mouth and ventral surface of the tongue is obtained, as well as the fimbriated sublingual and pterygomandibular folds, the lingual frenum and salivary caruncles.

Palpation is an important part of the physical examination and by running the index finger over the surface of the tissues, any irregularity can be felt. Pressure over a visible lump may elicit consistency of diagnostic significance. The alternate pressure of two fingers may produce the characteristic wave of fluctuation.

3. Radiographic Examination: is hardly necessary in diagnosis of white lesions of the oral cavity, unless the white lesion could be some manifestation of a general disease for which X-Ray examination would be helpful.

4. Laboratory investigations such as:

- (a) Blood counts, both F.B.C. and differential and Colour Index, bleeding and coagulation times, platelet count, etc.
- (b) Bacteriological Examination (Moniliasis, Syphilis)
- (c) Serological Tests (e.g. Syphilis)
- (d) Urine analysis (for diabetes mellitus) etc.
- (e) A dietary analysis (undernourishment)
- (f) Biopsy and smear tests.

should be carried out without hesitation, as necessary, to confirm or deny a tentative diagnosis. If these methods were employed more often, final diagnosis would be far more accurate than it, unfortunately, is in times when this need not be so.

The writer acknowledges the following further references which have been helpful in forming this introduction:

Bernier (1959); Blake and Trott (1962); Bolden, T.E. (1960); Cahn (1936); Cahn and Slaughter (1962); Colby et al (1961); Dummett, C.O. (1960);

Fleming (1958); Glickman (1958); McCarthy and Shklar (1964);
Noyes, F.B. (1960); Orban (1962); Orban and Wentz (1960); Reade (1961);
Rushton and Cooke (1959); Shafer et al (1963); Sognnaes and Albright
(1958); Whitelock (1960).

SECTION 2.

ABNORMALITIES OF EPITHELIAL COMPONENTS

- A. EPITHELIAL HYPERPLASIA
- B. EPITHELIAL KERATOSES
 - i. Hyperplasia with (hyper)keratosis
 - ii. Hyperplasia with parakeratosis
 - iii. Hyperplasia with dyskeratosis
- C. CARCINOMA-IN-SITU
- D. SQUAMOUS CELL CARCINOMA
- E. LEUKOEDEMA.

ABNORMALITIES OF EPITHELIAL COMPONENTS

A. EPITHELIAL HYPERPLASIA

A congenital lesion or lesions observed usually on the attached gingiva, the cheek and the palate, is a hyperplasia of the epithelium without abnormal keratin formation. The whitish patch, due to the thickness of the epithelium, is usually slightly elevated and well demarcated from its surrounds. It is firm, sessile and often stippled (Orban and Wentz, 1960).

McCarthy and Shklar (1964) speak of congenital epithelial keratoses and those keratoses must not be confused with this condition. At biopsy it would be seen that there is an increase in the thickness of the entire epithelial layer, with normal or perhaps slightly increased keratin. The submucosa is fibrous and free of inflammation.

Total excision at biopsy is advised: the condition gives no pain and causes no inconvenience, but it is felt safe to treat the lesions thus. However, these lesions are rare.

B. EPITHELIAL KERATOSES (According to Kollar et al, 1954)

(General Description and Definition)

These conditions frequently are, and have been, regarded as specific clinical states, known collectively as "Leukoplakia" (see Introduction). Shafer, Hine and Levy (1963) regard Leukoplakia as a white plaque on the mucous membrane, "specifically excluding all definite entities manifesting as white lesions, such as lichen planus, syphilitic mucous patches, white sponge nevus, moniliasis, lupus erythematosus, chemical burns and other stomatides". Clinically, however, some chemical burns, irritations or lichen planus, for instance, manifest themselves as a white patch or patches very similar to this so-called "Leukoplakia". Confusion must result: the author feels that it would be presumptuous to use the term "Leukoplakia" other than as defined in the Introduction.

Kinney and Derifield (1956) use the term "pachyderma oralis" to designate White Sponge Nevus, which latter term was used by Cannon in 1935. However, as Shafer, Hine and Levy state "pachyderma oralis" is often used to describe just a "white plaque" or a hyperkeratosis: just another possible source of confusion.

Colby, Kerr and Robinson (1961) state that the question as to what white patches should be biopsied is often asked. They emphasise that "histologic examination should be made of all such lesions which persist after removal of local irritants". No amount of clinical experience, they say, should enable one to rely on the clinical diagnosis alone. Firstly a consideration of the histology of epithelial keratoses must be undertaken, as this is the method of differentiation.

Histopathologically, keratosis is an increase in keratin on the surface of the mucous membrane in the form of parakeratosis and/or hyperkeratosis.

Hyperkeratotic changes in the epithelium are generally associated with hyperplasia but Cahn (1936) stated that they may accompany atrophy of the epithelium. Papic and Glickman (1950) observed a notable trend toward diminished keratinisation with increasing age and in the menopausal period. However, Montgomery (1951) and Iusem (1950) reported an absence of cyclical trends in the keratinisation of the normal gingival mucosa of the female, which was also confirmed by Papic and Glickman. There is no loss of polarity of basal epithelial cells or no basal-cell hyperplasia (and an inflamed corium is usually not present) where epithelial hyperplasia without dyskeratosis exists. Turesky (1961) in a study of 80 oral lesions diagnosed clinically as "leukoplakia" concluded from a histochemical viewpoint that hyperkeratotic lesions were characterised by an increase in disulphides and a diminution in sulphhydryls in the stratum corneum, which did not occur in parakeratotic lesions. In parakeratosis, the over-all thickness of the epithelium was invariably greater and hyperplastic epithelial pegs occurred more frequently than in hyperkeratosis. Glycogen interpreted as indicative of cellular activity, was generally confined to the parakeratotic lesions (Cahn et al, 1962). Thus, in these latter lesions, the rapidity of cellular activity would not permit time for the structural and chemical differentiation required for hyperkeratosis.

It should be remembered, however, that there is always some degree of keratin present on the surface of normal oral epithelium

and this varies according to location and conditions. It is increased, for instance, by frictional irritation such as chewing or brushing. The author feels it would not be good procedure to presume a diagnosis of "hyperkeratosis" clinically for, say, a white lesion on the tongue thought to be caused by friction from gingival calculus, for instance, until on removal of this calculus, the lesion disappeared. Up till this time, the use of "Leukoplakic patch" would be better - a biopsy should be performed if there was failure to disappear - if the lesion did "heal", the use of the term "Hyperkeratosis" is probably justifiable.

Orban and Wentz (1960) use the terms

- (a) "hyperkeratosis simplex" to describe what is defined by Sprague as "focal or diffuse keratosis without dyskeratosis", and
- (b) "hyperkeratosis complex" to describe what is defined as "Dyskeratosis with atypism".

They call the "hyperkeratosis complex", leukoplakia, thereby considering the term "leukoplakia" to define either a premalignant condition, or if "carcinoma in situ" exists, a malignant neoplasm, which definition does not satisfy this reviewer at all. However, the terms hyperkeratosis simplex and complex seem reasonable, provided "simplex" is understood to describe a lesion's status quo, by which it is meant that "simplex" could turn to "complex" - the former should not be taken lightly.

Cooke (1964) felt that the term "leukoplakia" be retained, but that the adjectives "non-dyskeratotic" and "dyskeratotic" be used to

describe the two forms of hyperkeratosis. Cooke objected to "simplex" and "complex" as descriptions because the terms "have no generally acceptable histologic connotation". The writer feels this argument is purely academic, as both suggestions, Cooke's and Kollar's, are a step in the right direction, but Kollar's, in the opinion of this writer, is the better description.

Cahn (1961) defined dyskeratotic epithelium by the word "disquiet". This may describe or convey a "potential" change to many - "bursting at the seams" is the better expression for those who believe that hyperkeratoses are to be always regarded as possible cancers of the future.

Using the term hyperkeratosis complex, which features dyskeratosis with atypism, the condition could be regarded as likely showing preneoplastic or even neoplastic disturbances in the maturation of the full thickness of the epithelium. There would be:-

- (1) Loss of, or serious disturbance in, the polarity of the basal epithelial cells, which could vary also in shape and size.
- (2) Some degree of basal cell hyperplasia.
- (3) Keratinisation occurring prematurely in individual cells of the basal or deep prickle cell layers.
- (4) Increased and often abnormal mitoses.
- (5) Prominent eosinophilic nucleoli.
- (6) Variation in degree of hyperchromatism among the basal and deep prickle cells.

- (7) Alteration in the nuclear-cytoplasmic ratio.
- (8) Dyskaryosis or nuclear atypism.
- (9) Poikilocarinosiis, or division of nuclei without division of cytoplasm.
- (10) A still intact basement membrane
- (11) Usually, inflammation of the sub-epithelial connective tissue.
- (12) Increase in surface keratin as parakeratosis and/or hyperkeratosis to produce clinically the white patch.

A severe atypism in dyskeratosis would blend into carcinoma-in-situ, which demonstrates typical bizarre cells throughout the full thickness of epithelium.

2. Occurrence and Incidence.

Orban and Wentz (1960) found that, in their studies and observations, 75 per cent of the sufferers affected by hyperatosis were males and the average age was between 50 and 60 years. Cooke (1964) said that "leukoplakia" is a pre-cancerous state in at least 10 per cent of all its lesions, but was pre-cancerous in 30 per cent of those lesions featuring dyskeratosis, which latter condition cannot be judged from the clinical appearance.

Breed (1964) examined 113 patients with leukoplakic areas of the oral cavity - of these, 27 had carcinoma. Ninetyone of the one hundred and thirteen patients were men and twenty-two were women. In seven, dental disease was thought to be a causative factor, while forty-nine were addicted to tobacco in some form. The average age overall was

fifty-seven years, so it was concluded that this keratotic condition was one of middle or later life. Of the twenty-seven patients with associated malignant disease, nine developed multiple cancers varying from two to five in number.

The buccal mucous membrane was involved in 51 per cent of the 113 patients, the tongue in 39 per cent, the gingiva in 19.5 per cent, the floor of the mouth in 5.3 per cent and the lip in 7 per cent. In 48 per cent multiple sites were present. Where known, the range of duration of disease extended from one month to thirty years. Breed states that subsequently sixteen further intra-oral cancers developed, making forty-three in all. He does not state what period of time elapsed in the progress of the white lesion to cancer.

Tiecke and Bernier (1954) have attempted to analyse the potential malignancy of lesions according to location in the mouth. As stated earlier, they too felt that dyskeratosis must be present for potential or real malignancy. The writer feels that location would play an important part, initially, simply because a lesion at the root of the tongue would not be seen, or its presence noticed by the patient, himself, whereas one on the lip would be readily observed. Again, susceptibility or proximity to irritation would play a part. Finally the ability to treat the lesion without causing incidental deformity with the treatment of choice is important, for surgery may sometimes be preferred, say, to radiotherapy, but because of location the latter must be used, or at least tried, for a while, with possible resultant radionecrosis of bone and surrounding tissues.

Renstrup (1958) investigated ninety patients with confirmed white keratotic lesions of the oral mucosa. The lesions were diagnosed at biopsy and he averred the impossibility of diagnosing clinically what is only diagnosable microscopically. The lesions, he found, were most often situated on the buccal mucosa, then the alveolar ridges, the dorsum of the tongue, the lips, the hard and soft palates, the sublingual area and the gingivae, in that order.

In their examination of 103 patients with hyperkeratoses, Fasseke et al (1959) found that:

- (1) Thirtyseven suffered from lesions of the (buccal mucosa) soft tissue.
- (2) Thirtytwo suffered from lesions of the (gingivae) jaws.
- (3) Ten suffered from lesions of the lips.
- (4) Nine suffered from lesions of the tongue.
- (5) Six suffered from lesions of the alveolar process.
- (6) Six suffered from lesions of the soft palate.
- (7) Three suffered from lesions of the hard palate.

It can be seen from the previous data that hyperkeratoses:-

1. Occur mostly in men.
2. Have certain sites of predilection such as the buccal mucosa and tongue.
3. Occur in the older age group.

and these statements are confirmed almost universally. It has been shown (Russ, 1957) that there is a definite decrease in normal gingival keratinisation in aged men and that, in this ageing process, the tissue therefore lacks a protective layer of keratinised cells. This lack renders the tissue more susceptible to mechanical, chemical or bacterial irritation.

Is it then, that the common keratoses seen so often in the natural ageing processes of the skin are similar in type to the keratoses in the mouth (which are white due to continual wetness) and that both are due, initially, to this lack of keratin production, followed by over keratinisation as a result of a chronic irritation of some kind?

Cooke (1964) felt that there were two other distinct clinical forms of (what he called for want of a better name) "leukoplakia" most closely allied to the pre-cancerous state, both generally unrelated to obvious external irritants such as smoking or friction.

The first he called Acute Leukoplakia (after Ward), a lesion of short duration and, therefore, he felt of greater malignancy potential. The second he called Senile Keratosis, which is a long standing keratinisation of a generally atrophic mucosa, sometimes associated with patchy melanin production. This latter condition, if accepted, would answer the writer's question above.

3. Clinical Features

(a) Hyperkeratosis Simplex is an irregular smooth white patch or patches which appear(s) dry and may be raised on a non-erythematous base. The lesions may be in the floor of the mouth, ventral surface and dorsum of the tongue, cheeks, palate, lips or gingiva.

It is stated by Orban and Wentz that white lesions appearing in the oral cavity in a symmetrical pattern should be considered congenital.

West (1962) feels the term "leukoplakia" has its greatest

significance as a clinical rather than a histological entity. Hyperkeratoses may be surrounded by tissues of normal base, as stated above, or by red inflamed tissue. He states that a white lesion is the result of either a decrease in the vascular supply through which the blood supplies colour to the tissues, or an increase in the distance between the capillary bed and the surface. The latter may be due to an increase in fluid cells, cell products or debris. Trauma, necrotic membranes or microbial growths can all change a tissue's colour.

Often painless, white, smooth, soft lesions may be unnoticed by the patient and only pointed out during a clinical examination.

(b) Hyperkeratosis Complex, often leading to carcinoma-in-situ, appears as an irregular grey-white plaque, possibly roughened or cracked, with ulceration frequently occurring. In the case of carcinomata-in-situ, a reddish appearance may be seen in lieu of a white plaque. Shafer and Waldron (1961) in their series on carcinomata-in-situ, found approximately half of the lesions exhibited no individual cell keratinisation, no epithelial pearl formation or hyperkeratosis. Hence the flat, velvety red appearance occurring, they said, anywhere in the mouth.

Cooke (1964) again using the term "acute" to describe an abruptly appearing and fast growing hyperkeratosis, warned of its potential malignancy, for, in two cases he examined occurring in this manner, both showed either carcinoma-in-situ or extreme dyskeratosis.

There is no clinical way, however, of distinguishing between the simplex and complex forms. Most authors mention a verrucous

"leukoplakia", a papillary type, usually seen on the lip, alveolar ridge, floor of the mouth, or palate.

4. Aetiology: This is often idiopathic - often the cause is congenital.

Denture irritation and X-Ray radiation may lead to the production of white lesions. Physical rubbing or injury, as in tongue biting or cheek irritation often produces the lesions. Heavy smoking, due to burning and chemical action, can lead to a whitened palate, or be more localised to small circumscribed areas. The former condition is known as "nicotine stomatitis".

Cooke (1964) felt that friction would appear to be the all-important factor, acting alone or in a combination with smoking or betel-nut chewing. He stated that the general improvement in dental care in the United States of America, Europe and Britain, resulting in fewer sharp teeth, was the reason why hyperkeratoses did not become malignant as often as in areas where teeth were neglected.

Systemic disturbances such as syphilis may predispose to keratotic lesions and will be dealt with separately.

Dyskeratosis may ensue from a condition of keratosis with only hyperkeratosis and/or parakeratosis exhibiting; there could be unfavourable hormonal, nutritional, systemic or genetic factors involved in the so-doing.

Hyperkeratosis associated with excessive smoking is, in Cornbleet's (1962) opinion, no different in histological appearance from idiopathic hyperkeratosis. He stresses regular examination of the patient.

McCarthy and Shklar (1964) state that the role of Vitamin A deficiency in the production of hyperkeratosis of human oral epithelium has not yet been clarified.

Waldron and Shafer (1960) suggest the possible role of Avitaminoses A and/or B in the aetiology of leukoplakic lesions, but add that there is little current support for these possible causes, or the role of endocrine dysfunction, in the production of white plates.

Nevertheless, most workers, including Bhaskar (1961), agree that iron-deficiency anaemia produces atrophy of the oral mucosa, which may lead to hyperkeratoses due to irritants such as smoking, mechanical trauma, etc. The clinical picture of the Plummer-Vinson syndrome may be manifest, giving rise to the atrophic changes, dysphagia and koilonychia (McCarthy and Shklar, 1964). The iron-deficiency state may be due to:

1. Insufficient intake of iron
2. Defective absorption of iron.
3. Increased loss of iron.

Clinically, too, there may be cracks or fissures at the corners of the mouth, a lemon-tinted skin and mucous membrane pallor, and atrophy of the lingual papillae (Shafer et al, 1963). Achlorhydria, chronic hypochromic anaemia and frequent splenomegaly are found.

The reason for the iron-deficiency must be found and the condition remedied with all haste.

Fasske et al (1959) state that in most instances of oral hyperkeratoses, there seems to be an exogenic cause such as chronic mechanical trauma, ill-fitting dentures and smoking or an endogenic

cause, such as metabolic disturbances (i.e. diabetes mellitus), although in more than fifty per cent of patients, neither exogenic nor endogenic factors could be established with certainty. This "idiopathic" type of hyperkeratosis occurs mainly in aged patients, almost as often in women as in men. A survival rate of 20 per cent was their finding.

Galvanic action was held by many to be a possible cause of hyperkeratoses, but this has not definitely been demonstrated (Fillings and Leukoplakia, 1959). Both Farrell (1958), and Inovay and Banoczy (1961) found that in many mouths electrical potential differences existed because of galvanic couples set up by dissimilar metals. The latter found that in some cases, leukoplakic conditions, presumably hyperkeratoses, which had been "incurable" by normal methods, responded to the removal of any existing, harmful high potential, the gravity of pathologic changes in the mucous membrane being not always in proportion to the magnitude of the potential difference; the individual response of the organism was decisive.

Lain and Caughron (1936) had concluded that in every mouth in which there have been placed two or more differing restorative metals, i.e. electro-chemically dissimilar, there has been established a galvanic battery which serves as a chronic irritant. This condition may cause lesions of many kinds, one of which could be a hyperkeratotic condition, "even ten to twentyfive years after the elements constituting an electric battery have been placed in the mouth". Proof of this statement would be difficult to establish and to this writer, it seems a very sweeping assertion. Lain and Caughron also had added that even

in the event of removal of the cause, a hyperkeratosis would not disappear immediately or even at all. They called for a realization of the seriousness of this difficult problem and common condition of oral galvanism.

Roome and Dahlberg (1936) had reported a case about the same time, in which an ulcer occurring in the mouth had been found not due to mechanical factors, etc. The ulcer recurred after initial excision, but disappeared when two fillings of dissimilar metals joined in the one tooth were covered with cement - it promptly recurred on removal of the cement. It was thought to be the result of galvanic action and is an example of the theory applied in aetiology of some hyperkeratoses.

Burket (1961) states that as these lesions are found near amalgam fillings usually, it appears likely that allergic reactions to metallic ions are the cause of the so-called electrogalvanic lesions and that they are an unlikely cause of any malignancy.

5. Diagnosis:

Kollar et al (1954) concluded that the term "leukoplakia" should be discontinued as a diagnostic entity and have classified maturational disorders in the epithelium of the oral mucous membrane as follows:-

- (1) Hyperplasia
- (2) Hyperkeratosis
- (3) Hyperkeratosis and inflammation
- (4) Hyperkeratosis, dyskeratosis and inflammation
- (5) Intraepithelial cancer
- (6) Epidermoid Carcinoma.

In the microscopic diagnosis of clinical white lesions, histological terms, as used above and as proposed by numerous workers in the field, would overcome confusion in terminology and diagnosis.

Szerlip (1961) stressed the importance of biopsy in diagnosis of white lesions and quoted Kollar (and Fish) in their tenet that dyskeratosis, while not necessarily leading to malignancy, must be suspect. It is of great importance to keep in mind, says Bradley (1956), that a white keratotic lesion may become malignant - he believes in surgical removal if no other method of treatment succeeds. Also in 1956, Moser stated that the change from a leukoplakic condition of keratosis to the malignant state does occur, but that more statistical data is needed. Shafer, Hine and Levy reaffirm this statement. Cooke (1964), as stated earlier, said that "leukoplakia" is a pre-cancerous state in at least 10 per cent of all its lesions, but was pre-cancerous in 30 per cent of those featuring dyskeratosis, which latter condition cannot be judged from the clinical appearance.

Kollar et al felt that biopsy of all "whitish" (they do not use the term "white") lesions is not necessary if differential diagnosis can establish beyond reasonable doubt that the condition is some specific entity other than a disorder in epithelial maturation; if unable to establish this, a biopsy should be employed. Shafer et al. stated that many hyperkeratoses cannot be differentiated from other specific white oral lesions without biopsy and that there should be no hesitation in establishing the diagnosis by this means.

In an article on intra-oral leukoplakia and associated carcinomata,

Silverman and Ware (1960) pointed out the extreme variation which may occur between the clinically observed intra-oral white patch and the histologic appearance of the tissue. Prediction of the histology has been unsatisfactory. They felt that indications for biopsy have been shown to be ill-defined. Furthermore, false negative biopsies are sometimes obtained which confuse the diagnosis, occurring because only a small portion of the entire lesion has undergone malignant change at the time of biopsy. They therefore urged more extensive biopsies of a serial nature as well as post biopsy "follow-up".

Burket (1961) suggested a tentative clinical diagnostic test for leukoplakic lesions by the application of Lugol's solution to the involved area and stated that areas of hyperkeratosis manifesting as clinical white lesions will not take the usual deep mahogany stain because of the decreased glycogen content of the cells comprising the lesion.

Joester and Morgenroth (1963) favoured the Papanicolaou method for exfoliative cytology in diagnosis, as the patient suffers no pain or discomfort.

Silverman and Ware also stressed the importance of exfoliative cytology, pointing out its accuracy, speed, simplicity and painlessness.

This writer concurs, as the technique offers cellular evaluation, extensive sampling of the lesion and uncomplicated future observations; it must be pointed out, however, that false negatives (or false positives) can occur, as in biopsy.

Renstrup (1963) described a method of estimating epithelial mitotic activity and also comparing the findings regarding this activity within

the two groups of oral leukoplakic lesions classified histologically, in his article, as hyperparakeratosis and hyperorthokeratosis, which correspond respectively to the hyperkeratoses simplex and complex of Orban and Wentz. His method is a modification of Marthaler's technique in which the mitotic activity is expressed in terms of number of mitotic figures per unit length of basement membrane. Previous studies of oral mucosa dealing with mitotic activity have utilised the so-called "mitotic index" which indicates the number of mitotic figures found per thousand counted cells. This latter method was considered poor, as the oral keratoses sometimes exhibit increased density of cells in the basal layers, often associated with epithelial hyperplasia. Also the presence of lymphocytes and plasma cells can make it difficult to distinguish nuclei for cell counting.

In these methods, the higher the mitotic activity, the higher the potentiality for malignancy.

Most workers are agreed on the use of biopsy as the only way in which to establish diagnosis: they mostly all agree too, that microscopic terms are essential in describing keratotic lesions. They differ at times only on the question of "potential" with regard to malignancy.

Tiecke and Bernier (1954) believed the presence of dyskeratosis is essential to the occurrence of potential or real malignancy and without this, label a lesion of hyperkeratosis as "pachyderma oralis". Sutherland (1959) wrote of "leukoplakia" as a specific condition, even differentiating it from hyperkeratosis, but mentioned that in order to reach a diagnosis, a biopsy must be taken - he held the view that "leukoplakia" is a white lesion showing dyskeratosis. In other words, it could only be demonstrated as such microscopically.

Hellinger et al (1963) agreed with Sutherland in this and even suggested that the term "leukoplakia" should be applied also to those cases in which a lesion is "clinically abnormal in appearance and/or occurs at an unusual site". It is felt that this last statement is completely presumptuous, because, as they themselves state, "the term 'leukoplakia' traditionally implies a potential malignancy". Therefore lesions occurring in unusual sites or appearing different clinically, are presumed potentially malignant.

Even the term "leucokeratosis" which they suggest for white lesions in "normal" sites and "normal" in appearance, is also presumptuous from the "keratosis" angle (a lesion may appear white without keratin formation) and "leuco" seems superfluous, as hyperkeratic formation is always demonstrated in the mouth by a "whitish" appearance.

Their study was an attempt to justify a correlation of clinical impression with the histologic appearance and aetiological agents. The author found it very stimulating, but it is felt that their proposals would only add to some present confusion.

Bernier (1955) also suggested the term "Pachyderma Oralis" for the hyperkeratotic lesion lacking dyskeratosis and this is defended by Shira (1964). Shira felt that the classification of the keratoses by Kollar et al. has merit, but "it is rather unwieldy and possibly may be more detailed than necessary". This author could not disagree more with the last statement. With the uncertainty of aetiology and prognosis of many keratotic white lesions, "detail" is essential.

6. Differential Diagnosis.

Diener (1961) reported a case in which there were white lesions bi-laterally, stated to be of seventeen years duration and which had increased in area year after year. There was no pain sensation from the lesions but there was soreness associated with a partially impacted upper left third molar. The author feels here that a significant point is the age of this patient, namely twenty-one years, considering the seventeen years duration of the lesions. There were no observable predisposing causes whatsoever. All four third molars were present and none was impacted except the previously mentioned upper left one. Both right third molars were unerupted. To remove all possible chronic irritations, it was decided to remove all four molars, and since conduction or infiltration anaesthesia was inadvisable, because of the white lesions, endotracheal anaesthesia was used. Post-operative roentgen irradiation was planned. However, five weeks after the operation, all symptoms of "leukoplakic areas" had disappeared. Diener felt that although the third molars were not apparently irritant, they must have placed the buccal mucosa in a susceptible state. He concluded that "in all cases of leukoplakia buccalis, the dentist should take into consideration the condition of the third molars and decide whether the immediate extraction of these teeth is indicated".

The author feels that the conclusion is vague insofar as, from this unusual case, one is not given any criteria on which to base a possible causative factor associated with the third molars, except their "erupting" presence. It could be that the patient was in the habit of cheek biting prior to eruption and this was manifested by

hyperkeratin production. Also, if symptoms had been present for some seventeen years, there must have been other previous causes involved in the production of the lesions - have they always been associated with previously erupting teeth?

This case has been included to make a point and it is well said by Cooke (1957) that there is a tendency to classify all white patches on the mucosa as hyperkeratoses. He stressed the importance of differential diagnosis in "leukoplakic" conditions, stating that congenital anomalies of the mucous membrane have not received the same attention as those of the skin. He felt the atrophic form of lichen planus (q.v.) is often confused with hyperkeratoses. Could not the case just described have been a congenital abnormality? There was no mention of a biopsy.

Differential diagnosis should take especially into account, (as well as lichen planus, congenital lesions and carcinoma previously mentioned) discoid lupus erythematosus, leukoedema and moniliasis, plus traumatic lesions. These conditions will be dealt with later.

Fasske et al (1959) examined 103 patients with hyperkeratoses and, for comparison, employed specimens taken from 40 patients with diagnosed oral carcinoma and 442 patients with other pathological alterations of the oral mucosa. Histochemically, biochemically and using electronmicroscopy, they reached the following four (4) conclusions:-

1. In all instances of oral hyperkeratoses, the basal cells of the surface epithelium show a large number of mitochondria and a lamellar structure, but few tonofibrils within the cytoplasm.
2. During cornification, an increase in the number of tonofibrils

takes place simultaneously with a decrease in the number of mitochondriae.

3. The basal cells decompose glycogen under an aerobic condition, but the epithelial cells contain glycogen deposits which subsequently are used as energy sources for differentiation processes.

4. During the cornification, keratohyaline is formed resembling the material of the stratum granulosum epidermis. At the same time, the glycogen disappears and the stored saccharides are used up. This process is promoted by the adenosine triphosphate and phosphatase of the cell nuclei.

7. Therapy.

The elimination of all possible factors of irritation should be undertaken. Sometimes this may result in the disappearance of a lesion, but observation should be carried out at regular intervals. Prognosis is good if a cause is found and removed and causative factors may be local or systemic.

Removal of a lesion by surgery, electrocautery, fulguration or dessication has been proven satisfactory at times.

Shafer, Hine and Levy recommend discontinuance of the use of tobacco and/or alcohol, correction of any possible malocclusion, replacement of ill-fitting dentures etc. This, they feel, is of more possible benefit than systemic factor elimination which can include Vitamin A or B complex therapy, estrogens, etc. They state that X-ray radiation therapy is not advised.

Estrogenic hormones and their stimulators have an apparent beneficial effect on the gums, stated Ziskin (1938), yet he warned of the probable side-effects.

Cornbleet (1962) regarded radiation therapy as acceptable but that it should be expertly done. Sutherland (1959) favoured radiation therapy as a means of treatment for either "predisposed" malignancy or actual malignancy in white oral lesions. Breed (1964), unlike Shafer et al, Orban and Wentz, etc., felt that early cancer developing in a patch of keratosis, may be destroyed by the surface application of radium because the cancer is superficial. He stated that a good vascular tumour bed is essential. However, surgical assistance had to be called upon, he said, in 11 patients of 27 treated with radium and this surgery was not effective in any of the nine patients he was able to trace later.

McCarthy and Shklar (1964) stated, with others, that a "stripping" operation is preferred by many surgeons and this procedure is acceptable since the lesion is not invading and the surgery does not penetrate deeply into underlying connective tissue - radical surgery is not indicated. Most authors agree that plastic grafting may or may not be used, depending on circumstances.

Herman (1961) found that in five cases of men treated with Vitamin A for "leukoplakia nicotina palati" at the Dental Clinic of the Free University of Berlin, four were successful, surgery being employed for the remaining one. These cases, he said, were caused by heavy smoking and he felt that only the discontinuation of the habit

will lead to complete cure. He gave a quantitative definition of "heavy" smoking (50 gms of pipe tobacco or more daily, two packets of cigarettes, etc.) but it is felt that this depends on the susceptibility of the individual, the author having seen mouths with this condition under widely separated degrees of tobacco addiction.

It has been indicated that work should be done on the local treatment of hyperkeratoses with Vitamin A (Leukoplakia, 1962).

Joester and Morgenroth (1963) examined one hundred and twenty-four patients who had had white keratotic lesion previously removed surgically, and twenty recurred. Of course, there could always be further recurrence in others at later stages. The tendency to recur indicates the importance of continued observance of these lesions and Tiecke and Bernier (1954) stated that carcinoma of the mouth is usually preceded by a long standing hyperkeratosis, which is resistant to treatment.

8. Conclusion:

Russ (1957) felt that further research is needed in at least the following:-

- (1) The comparative value of the present methods of treatment.
- (2) Experimental studies to determine whether hyperkeratoses will regress spontaneously when the causative agent is removed. (It is felt, however, in most cases, that it is impossible to find a real cause).
- (3) Experimental studies to determine whether hyperkeratotic lesions can be transplanted to another animal.

- (4) Further experimental studies to determine all possible abnormal changes taking place in the individual cells in hyperkeratotic areas.

C. CARCINOMA-IN-SITU

General Description and Definition:

This malignant condition is also known as intra-epithelial carcinoma or Bowen's Disease. It was first described by Bowen in 1912 and chiefly involves the skin.

Shafer, Hine and Levy (1963), speaking from a histopathologic point of view, stated that a definite distinction between dyskeratosis and carcinoma-in-situ cannot always be drawn. It is extreme dyskeratosis or really an "advanced" stage of dyskeratosis, exhibiting "top to bottom" change and particularly basilar hyperplasia. Shafer and Waldron (1961) found that in half the lesions diagnosed in their series as carcinoma-in-situ, there was no keratin formation of individual cells, no pearl formation or hyperkeratosis. They were described as flat, red, velvety and granular in appearance. Thus, the condition does not always present clinically as a "white lesion" and is often called an "erythroplasia".

There were once two views as to the nature of Bowen's disease:-

- (a) A pre-cancerous dyskeratotic lesion,
- or
- (b) A laterally spreading intra-epithelial type of superficial carcinoma.

However, Willis (1960) stated that Paget's Disease of the Skin, erythroplasia (of Queyrat) and Bowen's Disease are one and the same. He felt that individual cases show somewhat different clinical and microscopical appearances according to site, causation, preceding or

associated lesions and/or local mucosal peculiarities. "For the pathologist, however, there is only one entity, intra-epidermal carcinoma, the structural variations of which do not call for distinctive names".

Gibbins (1961) quoted Montgomery, who in 1939 stated that the term "pre-cancerous" dermatosis is used wrongly and misleadingly if a diagnosis is in doubt. It should be employed with great caution. Montgomery named four (4) specific entities to which the term could apply, but even this, it is felt, was not correct, as one of the entities was Bowen's Disease, a true cancer and another a state of "leukoplakia", which is not always pre-cancerous, even within the terms of definition of the word that Montgomery employed. He said that epithelioma resulting from so-called pre-cancerous conditions would begin first as carcinoma-in-situ.

Clinical Features and Occurrence: The lesions are equally divided between the sexes, in the opinion of Shafer, Hine and Levy, but usually occur in elderly people. Every oral "area" can be affected. Bhaskar (1961) agreed with this latter statement but feels that males are most affected by this condition. He said it is a white lesion usually, although stressing that it may be reddened, ulcerated or eroded, flat or elevated - it may be fissured, rough or smooth; any size, asymptomatic and may be increasing in size.

Gorlin (1950) cited eleven (11) cases appearing in the literature in which Bowen's Disease affected the oral mucous membrane. Of the eleven, nine (9) appeared in men and were found in different sites in the mouth.

Diagnosis: What has been previously applied to hyperkeratoses in diagnosis and in differential diagnosis, can be applied here, provided, of course, keratosis, forming a white lesion, is present. Sandler et al (1960), in an article on exfoliative cytology concerning objectively abnormal oral signs, namely slightly raised, moderately firm lesions on the lateral border of the tongue, pale surface lesions of the mandibular alveolus, soft palate, floor of the mouth, etc., stated that the greatest value of this diagnostic method "lies in its ability to disclose the presence of intra-epithelial or non-invasive oral carcinomas, when the clinical appearance is relatively innocent and cancer is not suspected." (Tiecke and Bernier, 1954). They confirmed the opinion of many others, including Montgomery and von Haam (1951) and Silverman and Ware (1960), that its utilisation prior to biopsy provides greater assurance of definite diagnosis as the cancer cells can be detected in a smear, while the biopsy specimen may not be adequate for diagnosis. This inadequacy has been pointed out previously when dealing with hyperkeratoses, but there, biopsy was more or less compared with exfoliative cytology as one method against another, whereas the above shows how the two are complementary.

Umiker et al (1960) concluded that the oral smear diagnosis of eighty (80) untreated carcinomata of the mouth and oropharynx was 96.3 per cent accurate. In the case of carcinomata-in-situ, with hyperkeratosis, it would be possible, however, to take smears without obtaining cancer cells, due to the presence of the keratotic layer. The cytological findings would show cells with pyknotic nuclei (parakeratosis) or no nuclei (hyperkeratosis) and not mirror the severe

alterations in the depths of the lesions.

Peters (1958) commented similarly on the results of smears from the mucosa of patients with oral white lesions.

Montgomery (1951) warned of the "rather drastic deviations from the normal cytologic pattern" occurring occasionally without apparent explanation.

Lesions, in which there was an early malignancy, could exhibit maximum nuclear abnormalities in the lower layers only. Thus as the cells progressed upwards, the nuclear atypism would become less and less, resulting in little or no abnormality in the smear (Umiker et al, 1960). This and the keratin cover aforementioned, helps, it is felt, to explain the deviations reported by Montgomery.

The role of cytodiagnosis is a "supporting" one in diagnosis. It would not, of course, give such information as the presence or extent of any invasion (Sandler and Stahl, 1958; Silverman et al, 1958; Pomeranz and Stahl, 1953).

Histology:

Intra-epithelial carcinoma is characterised by hyperkeratosis (usually), acanthosis, dyskeratosis and with all the signs of hyperkeratosis complex (Orban and Wentz).

Bhaskar (1961) said the only difference from hyperkeratosis complex is one of degree. Vacuolisation of some of the cells occurs. The important factor is the intact condition of the basal layer of the stratum germinativum, even though it is disorganised and often fails here to show normal palisading. Metastases would not occur, therefore, in intra-epithelial carcinomata, since the basal layer's intact

condition would preclude this happening, there being no connection between the malignant cells and blood or lymph vessels of the corium.

The corium itself is usually infiltrated with chronic inflammatory cells. Plasma cells and histiocytes are often seen.

Woodbridge (1950) in an article concerned mainly with the "invasiveness" of carcinoma-in-situ, quoted McCutcheon and Cowan, saying that cancer cells can produce the enzyme hyaluronidase in small quantities, but probably sufficient enough, and for long enough time, to act on the hyaluronic acid of the basement membrane adjacent and disrupt it.

She also pointed out how epithelial cells are normally cemented by an intercellular substance allowing movement one to the other, but preventing separation. Calcium lack decreases adhesiveness and this adhesion is not restored when the element is replaced. Woodbridge then quotes Zeidmann, who stated that cancer cells are low in calcium; hence the lack of adhesion one to another, which, coupled with the statement of Arcand (Woodbridge) that cancer tissues have a diminished surface tension directly proportional to their malignancy, adds to cellular mobility and invasiveness.

Treatment:

This is best done by totally excising the malignancy with a definite margin of apparently normal tissue. Radiation has been used, as well as cautery and solid carbon dioxide, although Orban and Wentz recommended that Roentgen radiation and radium treatment not be employed (Shafer et al., Orban and Wentz).

Bhaskar (1961) stated that lesions of the floor of the mouth and of the tongue are most aggressive and that the prognosis here is not good.

Epidermoid carcinoma-in-situ is undoubtedly the microscopic change which often preceded invasive cancer. This microscopic change frequently is prominent around an invasive cancer. This fact must be considered in planning adequate surgical and Roentgen ray treatment. The speed of evolution of this lesion from intra-epithelial to invasive cancer is very variable (Ackerman and McGavran, 1958).

D. SQUAMOUS CELL CARCINOMA:

1. Introduction:

This cancer is also called epidermoid carcinoma and is the most common malignant neoplasm of the oral cavity (Shafer et al, 1963). It represents 90 per cent of all oral malignancies (Bhaskar, 1961). When involving a mucous membrane surface, it is much more prone to metastasise early than on the skin (Payling-Wright, 1958), with the result that the patient often presents with the regional lymph nodes enlarged. It is 8 to 9 times more frequent in males and occurs usually after the fourth decade, while Wynder and Bross (1957 A) are of the opinion that the incidence is four times greater in men, but that the site of occurrence governs the proportion. Great variation occurs in geographic distribution and in Bombay, 40 per cent of all forms of cancer in one hospital were oral squamous cell carcinomata.

Pindborg (1963) feels that the study of the epidemiology of oral cancer may contribute to a better understanding of aetiology. The frequency of oral cancer, he concluded, was 1 to 6 per cent of all tumours, the morbidity rate was from 2.7 to 21.1 per 100,000 population and the mortality rate was from 0.5 to 11.1 per 100,000 population. Marked differences in sex ratios were observed in different countries and he noted that in England, Canada, Australia, Norway and West Germany, decreases in mortality rates have been observed. However, in Denmark, no significant change in the oral cancer morbidity rate was found in a 14 year period.

While among the most accessible of cancers, it is one of the most fatal. It is essential to recognise the significance of early or pre-cancerous conditions, as total mortality among all cases remains about

75 per cent (Ewing, 1942).

Cahn and Slaughter (1962) stated that "whenever leukoplakia is thick, palpable and irreversible by ordinary measures, it must be removed or destroyed if at all possible. If removed surgically, the entire specimen must be processed through the pathology laboratory for microscopic evaluation. If not removed surgically, biopsy of multiple areas must be done.

Epidermoid carcinoma is more common on the lips than intra-orally, the lower lip being by far the more involved. However, when the mouth cavity is involved, the site may be anywhere such as on the tongue, (usually the lateral borders), floor of the mouth, alveolar mucosa, palate and buccal mucosa.

Squamous cell carcinoma may appear clinically in three broad separate categories - verrucous or papillary (see later chapter), ulcerating, or as a relatively flat lesion, deeply infiltrative. It is usually described as an ulcerating, fungating lesion, with indurated margins bound down to the underlying tissues; here, it is dealt with as a white lesion and, therefore, would in most cases, be in the early stages of malignancy.

2. Occurrence and Incidence:

Carcinoma of the Lip: Cross et al (1948) carried out an excellent review of five hundred and sixty-three (563) case records of lip cancer. The site of the tumours was most frequently on the lower lip: 497 on the lower, as against 19 on the upper lip, 47 being in the commissures, and despite the obvious location of the growth, the

median duration before advice was sought, was six months. 98 per cent of the patients were men, with the great majority aged between 55 and 75 years. The mean age of 62 years averages some years more than the age at which intra-oral cancer usually occurs. Most authorities seem to reach conclusions similar statistically to Cross et al.

However, in Scandinavian countries, where the Plummer-Vinson Syndrome is more common, it would be expected to have a higher incidence of oral carcinomata in women than usual, as will be mentioned later.

It is practically unknown in the Negro.

Clinically, the lesions can arise in areas of hyperkeratosis, but Cross and co-workers found this association in only 14.5 per cent of the cases in their series and others have found even smaller percentages. Actinic rays of the sun and pipe smoking are two possible causes.

Spatz (1964) described the condition of epithelial abnormality of the lip produced by the actinic rays of the sun as "Solar Cheilosis". Thoma and Goldman (1960) refer to it as "Actinic Cheilitis". Spatz said it usually occurs on the vermillion border and expansion in a linear, superficial manner has been frequently observed. Most writers feel that solar cheilosis definitely predisposes to a carcinoma. Spatz feels that 10 per cent of the cases with this condition originally will ultimately, if left untreated, metastasise and that the five year cure rate is only 80 per cent. An interesting report is that of Van Zile (quoted by Spatz), who described a series of 37 cases of Solar

Cheilosis in which approximately 50 per cent of the patients histologically had 2 to 5 separate malignant lip lesions, although only one (1) was usually discernible clinically.

Histologically, the tumour is mostly well differentiated and often does not metastasise till late in its course, if at all. McCarthy and Shklar (1964) reported a case that was followed for 15 years after therapy was refused by the patient. Whereas there was local involvement by invasion, no metastases occurred during the entire period. The upper lip, however, has a more unfavourable prognosis.

Squamous Cell Carcinoma of the Tongue is generally agreed to have a very poor prognosis, having a five year survival rate of about 20 to 30 per cent. Where lesions are detected early, a survival rate of 50 per cent could be expected.

Gibbins (1961) quotes Gibbel, Cross and Ariel, in a review of 330 cases of cancer of the tongue, stating that the better differentiated, keratinising cancers are usually found in the anterior two-thirds of the tongue. These anterior area tumours comprise 95 per cent of observed cases (The author feels "observed" here should be emphasised). The frequent site is a lateral border, cancer of the dorsum being rare, where it is usually due to a past or present history of syphilis. Shafer, Hine and Levy say that carcinomata on the lateral border is equally divided between the base, the mid-portion and the anterior third. Lesions near the base, of course, are particularly insidious and may be asymptomatic until far advanced.

Squamous carcinomata of the tongue is second in incidence in the oral region to carcinomata of the lower lip.

Carcinoma of the alveolar mucosa comprises 10 per cent of all intra-oral cancer, of the buccal mucosa 10 per cent, of the floor of the mouth 15 per cent and palate 10 per cent (McCarthy and Shklar).

All sites here may at first be manifested as white lesions. The percentages here for carcinomata do not tally well with the percentage occurrence of hyperkeratoses observed at corresponding sites in the mouth (see previously). There could be some significance in this.

Tiecke and Bernier (1954), in their excellent analysis, categorise the above primary sites of occurrence of carcinomata in percentages and these coincide remarkably well with figures in most writings on the subject, as well as the aforementioned statistics.

Prognosis is usually not very good and is, of course, governed by the site and access. Bhaskar (1961) says that about 5 per cent of squamous cell carcinomata present as white plaques, which may be flat, elevated or fissured and there can be, at presentation, adenopathy of submental, submaxillary or jugular lymph nodes.

3. Aetiology.

Shafer, Hine and Levy list as the most common aetiological factors in the development of squamous cell carcinomata:-

1. Tobacco)
-) use of
2. Alcohol)
3. Syphilis
4. Nutritional Deficiencies.

5. Sunlight (lip cancer)

6. Miscellaneous factors, including heat, trauma, sepsis and irritation from sharp teeth and dentures.

Tobacco smoking can produce nicotine stomatitis (hyperkeratosis), particularly when a pipe is used - this may be, in some cases, the precursor of squamous cell cancer. Alcohol also appears to be an important factor in aetiology, but whether by local irritation or systemic action is not known. Trieger et al (1959) feel that the local effect of alcohol on the oral mucosa may be of lesser importance and secondary to a generalised change in the mucosa via malnutrition and resultant hepatic dysfunction, for, in the group of 68 patients studied by them, there were some (the number is not stated) who were non-drinkers, but were suffering from cirrhosis of the liver. Malnutrition and hepatic disease is further suggested in the aetiology by the work of others. In India, where malnutrition is rife, oral carcinomata, as stated before, comprise a heavy proportion of all cancers.

Wynder et al (1957 B) found significant importance in both the use of alcohol and/or tobacco in the aetiology of oral cancer, as extrinsic factors. They felt that if both these factors were eliminated, four out of five cases of oral-cavity-cancer would be prevented.

Kreshover (1955) found that the cutaneous tissues of mice are rendered more susceptible to the irritating effects of whole tobacco smoke by a deficiency in Vitamin B complex. Riboflavin, pyridoxine and pantothenic acid are the components primarily responsible for such alterations in tissue response, whereas biotin, thiamine and nicotinic

acid deficiency do not seem to cause any greater susceptibility to irritation of the tobacco smoke applications than to mice on a normal adequate diet.

A summary of the work of Salley (1963) on the effects of smoking in the production of oral cancer is as follows:-

Studies were conducted to determine the effect of whole tobacco smoke (cigarette) on epithelial tissues of mice and hamsters. When daily applications of smoke were made to the ears and lips of mice for up to 80 days, ears demonstrated some dyskeratotic change. This effect was enhanced by concurrent Vitamin B complex deficiency. In no instance were lips altered by "smoking". Prolongation of experimental periods to 20-24 months of daily "smoking" extended these findings, but still no neoplastic changes were observed. Intra-oral smoke application to palate and pouch mucosae of hamsters for similar periods also resulted in no evidence of neoplastic disease. Studies of cigarette smoke and concomitant exposure to ultra-violet light (irradiation) had the same negative effect. However, when smoke was applied daily to oral mucosa that had first been treated with a suboptimal dose of a known carcinogen, squamous cell cancer resulted in 56 per cent of animals. Hamsters treated with the initiating dose of carcinogen only had a 24 per cent incidence of tumours. It appears that, in the oral epithelium, smoke is a cancer-promoting agent by chronic irritation.

Kreshover also found that gonadectomy renders cutaneous tissue less susceptible to irritation from whole tobacco smoke and that tissue response was not influenced by sex.

In an article published in 1952, some three years previous to his above studies, Kreshover had reported an absence of pathologic change in oral tissues subjected to similar applications of whole tobacco smoke, again using mice. He felt this suggested either a basic difference in response by different tissues, or a protective effect by the tongue and saliva in readily removing tars. Kreshover (1955) stressed that whereas the mice cutaneous tissues were affected, hamsters which he later used, subjected to twice as many smoke applications as the mice, were unaffected. He concluded with the warning that all species therefore do not react similarly and warned that it would be sheer speculation to apply such findings to man.

A possible relationship between aetiology and Vitamin A deficiency can be found in the work of some researchers, who were using Vitamin A in therapy. One example is as follows:-

Zegarelli et al. (1959) concluded in their work with 29 patients, aged 16 to 72 years, comprising 17 men and 12 women, that "our observations with these patients (suffering from leukoplakic oral lesions, all diagnosed as keratoses) were that the Vitamin A as administered frequently had an impressive, useful and beneficial effect on the lesions under treatment". Administration was in the form of troches, resulting in a topical, as well as a systemic, application, preferably sucked at the site of the lesion. Vitamin A was incorporated in the troches as the pure synthetic vitamin, 150,000 U.S.P. units per troche, and four (4) to six (6) troches were given daily. Therapy of at least three weeks' duration was required before any clinically significant therapeutic effects were observed.

They stressed the care to be exercised in the treatment of oral keratotic lesions from a "dosage amount" point of view and quote Hillman, who reported that the ingestion of an aqueous Vitamin A preparation in doses of one million units per day for a two week period resulted in toxic symptoms, namely gastro-intestinal disturbances, cheilosis and lip splitting, headache and dermatitis.

Thoma and Goldman (1960) and Shafer, Hine and Levy (1963) speak of the effect of nutritional deficiencies on the oral mucous membrane in relation to the Plummer-Vinson Syndrome, which is a form of iron deficiency anaemia. It is one of the few known predisposing factors in oral cancer and occurs mostly in women in the fourth and fifth decades. Oral signs are a red, smooth sore tongue with atrophic papillae, angular cheilosis and the mucous membrane of the mouth generally is atrophic.

The aetiology is due to:-

1. Chronic blood loss.
2. Inadequate diet
3. Faulty iron absorption.

The iron deficiency could be the cause of the atrophic state of the mucous membrane, which depends on adequate iron blood level for its well-being.

Wynder et al (1957) stated that the women of Scandinavian countries were more prone to oral cancer than those in most other regions because of the preponderance of this Plummer-Vinson Syndrome among them. But he also noted that Scandinavians often lacked

Vitamin C and felt this showed some evidence of a link in the aetiology of mouth cancer. The author feels here that if there was a Vitamin C lack among the women, it would also most likely be lacking in the men. Hence, if Vitamin C lack could be blamed as a causative, or predisposing factor, it would have to affect women and not men, otherwise the overall proportion found in other countries would have to be found in Scandinavia too, which, as stated above, is not the case.

Monto et al (1961) reported alterations in exfoliated squamous epithelial cells of the tongue in cases of severe iron deficiency anaemia, consisting of a deficiency in keratinised cells, alterations in nuclear-cytoplasm ratio, an increase in nucleoli, the presence of double nuclei and the fragmentation of some nuclei, pieces being scattered throughout the cytoplasm (karyorrhexis).

Colby et al (1961), Burket (1961), Payling-Wright (1958), Ewing (1942), Thoma and Goldman (1960) and Santis and Chauncey (1964) agree on the importance of sepsis and irritation and also trauma as causative agents in the production of epitheliomata. However, Wynder et al, do not find any significance in these factors as aetiological agents. The author feels, however, that though no direct part may be played in aetiology, at least a predisposing role seems to be probable.

As stated before, Wynder et al (1957 B) concluded in their excellent report on the aetiology of mouth cancer, that "trauma and dental irritation were not found to be significant factors in the development of cancer of the mouth." However, earlier, they qualified

this statement by saying that women have, more often than men, a tendency to recall factors that they believe may be associated with their disease: and this ties in with the fact that women could recall instances of traumatic irritation, while men could not.

Sage (1960), however, stated that chronicity is the important condition in the production of cancer when irritation is involved. In the usual single, acute traumatic or acute inflammatory process, destruction of tissue is followed by complete repair with new tissue and subsequent effects not resulting.

Willis (1960) said there is little or no evidence that syphilis, alcoholism and dental irritation are important causative factors. Willis favoured the conclusions of Haagensen and Molesworth that sunlight plays an important role in the aetiology of lip cancer. Wynder et al, too, had felt that sunlight appeared to be of aetiological significance only in lip cancer.

Stones (1962) stated that syphilis, as a causative agent, is now declining. However, syphilis, according to Wynder et al., is a definite predisposing factor in the development of cancer of the lip and the anterior two-thirds of the tongue. Whether the cancer is caused by syphilitic glossitis or by the arsenic therapy once used, is debatable. They also found that edentia was more common among mouth cancer patients, particularly in women, pregnancy having a significant influence on edentia.

Warburg (1956), in an article on the origin of cancer cells, gives two phases of production:

1. The irreversible injury to respiration, which in its turn can

be due to many factors such as the application of tar, rays, pressure, urethane, arsenic, etc.

2. Following this respiratory injury, a long struggle for existence by the injured cells to maintain their structure ensues, in which parts of the cells lose their energy, while other parts succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy, the highly differentiated cells are converted into undifferentiated cells which grow wildly: the cells of cancer.

Kuhnau (1958) stated that tumour cells were different from other normal cells due to the absence of certain proteins, present usually in normal cells as enzymes or structural elements. Therefore, due say, to the loss of a respiratory enzyme, the growth may become unco-ordinated. In the tumour cell, energy is then provided by a more primitive process termed "aerobic glycolysis" (Warburg). The inhibition of respiration in tumour cells is probably caused by the liberation of minute amounts of polycyclic hydrocarbons such as benzpyrene and methyl cholanthrene or related substances, which enter into chemical combination with respiratory enzymes and prevent necessary enzyme action. This could possibly happen through the agency of cigarette smoke, combustion products, etc. as "external" factors, and such "internal" factors as abnormalities in steroid (hormone) metabolism.

This hypothesis could explain many types of tumours. The reverse could occur, of course, a number of chemical substances being capable of blocking glycolysis and, therefore, suppressing a malignant course in cells during the pre-cancerous stage. These are the "cytostatic"

agents and this fact has been adopted in chemotherapy of malignant tumours, a method of treatment at present in the experimental stages.

Okamoto et al (1963) studied the histochemistry of aminopeptidase in 52 cases of oral tumours, but could not correlate enzymatic activity specifically with tumour growth.

The foregoing is in contrast to the mutation concept, which considers the altered cellular morphology and metabolism as manifestations of a basic chromosomal change, the pattern being passed on to succeeding generations following mitosis.

From all these findings it could be that cancer of the mouth is not caused by a single factor, but may be caused by two or more agents either acting locally or systemically, one perhaps rendering the tissue susceptible and another or others causing the actual cancer cell production. Even in the mutation concept, the "trigger" or "susceptibility rendering" factor may be inherited and the "cause", if applied to the susceptible tissue, could produce the malignancy. So perhaps the mutation concept may have a link with the respiration findings of Warburg. Weisberger (1957) stated that the response of the tissue to the irritant appears to depend on the host factor in the tissue cells.

It can be seen how difficult, therefore, it is to reach conclusions as to aetiology in this dread disease.

Histopathology:

All writers reviewed agree on the basic histopathology of what constitutes the malignant state of cells of squamous epithelium, and "invasion" is necessary for squamous cell carcinoma to be present.

Differences of interpretation of degree of malignancy are encountered, however. Shafer, Hine and Levy stated that highly anaplastic lesions do occur, but are rare. The usual well-differentiated carcinoma consists of sheets and nests of cells with obvious origin from squamous epithelium. These cells are generally large and show a distinct cell membrane, although intercellular bridges or tonofibrils often cannot be seen. Nuclei stain variably light or dark and mitotic figures are not necessarily numerous. The main feature is individual cell keratinisation and the formation of numerous "epithelial pearls" of varying size. In a typical lesion, groups of these malignant cells can be found actively invading the connective tissue in a vagarious pattern. The poorly differentiated carcinoma cells do not resemble the cell of origin and are different in shape, arrangement one to the other, growth rate (reflected in greater numbers of mitotic figures) and even more variation in size and staining characteristics - they fail to carry out the function of a differentiated squamous cell: keratin formation.

Broders, in 1926, described four grades of tumour, well shown in the squamous cell carcinoma, and the grade depends on the "differentiation" of the cancer, Grade I being well differentiated and grade IV being highly anaplastic, the other two grades being intermediate in differentiation. However, Ewing (1942) and Shafer, Hine and Levy mentioned the pitfalls of using this system from the point of view of prognosis, as gross anatomy, situation, age of patient and the fact that the same cancer may have different degrees of differentiation in varying areas, all could effect the outcome.

A descriptive grading from a histopathologic viewpoint seems the answer, in the author's opinion, to the categorising of tumours.

Santis and Shklar (1964), and Santis and Chauncey (1964) used histochemical methods applied to the study of malignant oral neoplasms to determine microscopically, if possible, the degree of malignancy or clinical aggressiveness of a given carcinoma. A decision to undertake a study to evaluate the basement membrane area, in cases of oral carcinomata, was reached. It had been previously reported by Cahn et al (1961) that, in fifteen cases of frank squamous cell carcinoma, the basement membrane no longer took on a heavy stain, using the periodic acid - Schiff method which can outline the membrane exceptionally well in a vivid magenta colour. The membrane was found to be "missing" in ten cases and "vague" in five. However, from the studies of Santis and Shklar and Santis and Chauncey it was apparent that basement membranes could be seen in invasive but well-differentiated carcinomata, whereas in cases of intense inflammatory infiltration and poorly differentiated carcinomata, the membrane appeared to lose continuity. They agreed with Ashworth and co-workers whom they quote thus: "The demonstration of intact basement membrane, either histochemically or with electron microscopy, cannot be unreservedly interpreted to indicate that a given nest of neoplastic cells is of non-invasive status". Santis and Shklar, though agreeing with this, as said, concluded that, though the basement membrane is present in Broders' cl. I Carcinomata, it is absent or fragmented in highly anaplastic lesions (Broders' cl IV). Therefore the P.A.S. stain may be of value

in the determining of degree of malignancy of epidermoid carcinomata. The author also feels the need for investigating whether a given cancer is of a pre-determined degree of malignancy from the outset and stays that way. In literature on the subject of surgical therapy, it has been stated that some carcinomata will increase in anaplasticity, invasiveness and general malignancy if the particular lesion is not initially fully removed - trauma of any kind has appeared to adversely affect some tumours, while others, not affected at one time, could be affected at another.

This could also be pursued by determining whether in "field cancerisation", the multiple lesions which often occur are of the same degree of malignancy. Meyer and Shklar (1960) investigated the problem of multiple lesions and concluded that the possibility of their occurrence was quite definite, all possible steps needing to be taken to prevent new lesions, such as removal of all irritations, etc.

Ackerman and McGavran (1958) stated that multiple cancers of the oral cavity are certain to increase in frequency (of detection), for as the effective therapy controls or cures the detected lesion(s), other cancers will arise in the remaining oral cavity mucosa. Therefore, follow-up of patients "cured" of one cancer of the oral cavity must be made because of the chance of developing another cancer, their opinion being that if a carcinomatous change takes place in the oral mucosa, its lateral spread is far greater than perhaps believed and, therefore, the initial removal is not wide enough. This could lead to possible so-called "secondary" sites of involvement, which are really not strictly secondary at all.

McCarthy and Shklar (1964) stated that "activation" of an oral-squamous cell carcinoma does not take place after biopsy. In their experience, the idea that lymphatic or blood borne metastasis is a problem in biopsy is also unfounded. It has been demonstrated that cancer cells are found in the blood stream after biopsy in greater numbers than before, i.e, the biopsy produced a "cell shower". But, they say, the mere presence of cells does not determine their capacity to develop malignant foci and, above all, the fact that an accurate diagnosis is possible from the biopsy, more than compensates for any possible "triggering" of rampant malignancy for, if carcinoma is diagnosed, immediate therapy would be instituted. They emphasised that they have not seen a serious result attributable to biopsy procedures, but have seen many deaths due to oral cancer which deaths might have been prevented if the diagnosis had been made earlier.

Cooke (1963) stated that his reasons for the use of exfoliative cytology in the diagnosis of oral cancer are:-

1. For screening large areas of abnormal-appearing mucosa, in order to choose the site for a biopsy in an area from which the most suspicious cells are found.
2. As a preliminary investigation for oral cancer in a patient too nervous to allow a biopsy.
3. For preliminary investigation of lesions, forming on the site of a treated cancer, to exclude a recurrence or a new primary.

He feels that exfoliative cytology usually plays a minor supportive role in a properly planned and carefully executed biopsy for the diagnosis of oral cancer. The definitive diagnosis is made by biopsy. -- In early lesions, as yet no investigator has shown exfoliative cytology to be of value in the diagnosis of non-ulcerative carcinoma of the mouth. In early cancer, it is the disturbed relationship of one cell to another that is important and these subtle changes can be observed only in tissue sections.

The author agrees and feels that in cases presenting as white lesions which could be possible malignancies, it is particularly important to have a biopsy examination: with ulcerating types of lesion, the clinical picture may be typical of carcinoma and biopsy may be unnecessary for an experienced clinician, although it is nice to be sure.

Biopsy, or histopathologic study, said Boyle (1954), is the only acceptable method for diagnosis, particularly in the early stages, of malignant disease. He stressed, however, that medicine and surgery have styles and fashions that seem right and proper while in vogue, but shortly afterwards seem illogical. At the present time, biopsy is "in fashion". The arguments for its use are valid, but the assumption that it is without danger is based on inadequate data. He felt that a biopsy should be done only by a specialist expert.

Tyzzar said long ago - "It would be better for the patient if each questionable lesion - - - - could be regarded as a high explosive, the least manipulation of which should be avoided at all costs".

4. Therapy:

Castigliano (1961) in an excellent article on oral (and other) cancer in which he deals with most aspects of the scourge, stresses the importance of combined radiation and surgical therapy in treatment. He urges follow-up or excision of "leukoplakia" according to biopsy, which, he says, is imperative if the condition worsens or fails to improve. Delay, he stated, is inexcusable. Radiation treatment of any great extent should be preceded by extraction of all remaining teeth, good or bad; irradiated teeth are prone to decalcification and can lead to infection. Dentures should be made with great care after irradiation therapy.

Radiation therapy by the external cone technique can produce excellent results in some cases. Meyer (1960) said that the use of supervoltage is becoming increasingly more popular as its advantages become demonstrated, Cobalt 60 being now widely used in the therapy of oral carcinomata. Meyer et al. (1963) have shown that Cobalt 60 radiation applied to the jaws produces considerably less osteoradionecrosis and soft tissue damage than 200 K.V. radiation.

McCarthy and Shklar (1964) feel that, in time, higher doses of supervoltage should produce even better results. There are cases in which surgery is preferred to radiation and vice-versa. There are cases, too, in which surgery and radiation in combination offer more than either method alone. Present-day therapy asks for a high degree of co-operation among all specialists involved. Lack of such unity of effort is responsible for many failures of treatment. Every case

should be treated on its merits (Low-Beer, 1951) and these sentiments were echoed in 1957 by James.

The author feels, however, that at present surgery should be employed where possible in the early stages of development, leaving radiotherapy for the inaccessible lesions. A neck-dissection can also be carried out in conjunction with either radiotherapy or surgery of the primary lesion, according to the site. If on the lower lip, less radical treatment would be needed than, say, in cancer of the root of the tongue or floor of the mouth.

Spatz (1964), in treating cases of malignant solar cheilosis, stressed the importance of complete removal of all possible manifestations by a horizontal surgical wedge operation with vertical components if necessary, stating that all incomplete efforts appeared to him to have increased the degree of anaplasia of the condition and created a false sense of security in dealing with a usually low-grade malignant lesion.

Renaud (1961) had found anti-tumoral, bacteriostatic and toxic effects were produced when neomycin was used in rats in high doses. Nothing further has been seen in the literature on this subject by this author. Perhaps the neomycin, which was not productive of the above symptoms in small doses, was acting purely as any poison could act i.e., it was toxic to all living tissue.

Conclusion:

This review has discussed keratoses and malignant change in oral mucous membrane only in so far as they remain as white lesions -

it has dealt with the problem mainly as a hyperkeratosis which, statistically, will either heal or stay as such, occasionally only becoming pre-cancerous or actually malignant; or it has dealt with this problem when it occurs as a malignant condition from its inception, but, again, only as a continuing white lesion.

E. LEUKOEDEMA: (Leukoderma: Burket, 1961).

This condition is a white lesion of the oral mucosa, of unknown aetiology. It is described as a disease entity by Kollar et al. (1954). Shafer, Hine and Levy (1963) quoted Sandstead and Lowe, who, in the Journal of the National Cancer Institute of the United States of America, found no apparent correlation between the incidence of leukoedema and the use of tobacco, the pH of the saliva, oral bacterial infection, syphilis or galvanic irritation. In their study, the incidence of leukoedema was approximately 45 per cent in white men and 40 per cent in white women, whereas in negroes it was 94 per cent in men and 86 per cent in women, the average age being 45 years.

Clinical Features: The gross appearance of leukoedema varies from a filmy opalescence of the mucosa in the early stages, to a whitish-grey lesion, later becoming wrinkled. The lesions usually are bilateral, frequently involving most of the buccal mucosa, being more noticeable along the occlusal line in the bicuspid and molar region. In some cases, desquamation occurs, leaving the surface eroded.

Gibbins (1961) said that, clinically, leukoedema appears to be an entity distinct from classical hyperkeratosis simplex or complex.

The mucosa appears oedematous, even waterlogged. There is, of course, obliteration of the vascular pattern of the submucosa which is visible through normal translucent epithelium.

Histologic Features: Microscopically, leukoedema consists of an increase in epithelial thickness, intracellular oedema of the spinous or Malpighian layer, an irregular, amorphous surface without keratin (McCarthy and Shklar, 1964), and broad rete pegs which appear irregularly elongated. The characteristic oedematous cells appear extremely large and pale and present a reticular pattern. The cytoplasm appears lost and the nuclei absent, clear or pyknotic. Inflammation of the corium is not usual (Shafer et al). The white appearance is not due to spongiosis but to parakeratosis.

The author has been unable to find any reference in journals as far back as 1954 or any significant literature in text books on the subject of leukoedema. Further work is therefore needed to investigate any possible connection between leukoedema and the keratoses. However, Burket (1961) stated that differential diagnosis is no problem; the tissues are flexible and manifest no change in their physical characteristics on palpation as compared with, say, hyperkeratosis. He stated that when there is wrinkling associated with leukoedema the condition may simulate lichen planus, but that the differential diagnosis may be made by stretching the oral mucosa, when leukoedema will disappear and lichen planus lesions will become more attenuated.

Therapy: Authors state that no treatment is indicated.

SECTION 3.

INJURIES AND BURNS TO THE ORAL CAVITY

PRODUCING WHITE LESIONS

- A. MECHANICAL INJURIES
- B. BURNS.

INJURIES AND BURNS TO THE ORAL CAVITY PRODUCING WHITE LESIONS

A. MECHANICAL INJURIES.

1. General.

The hyperkeratotic white lesions produced by physical or mechanical injuries have been presented in the sections on hyperplastic and/or dystrophic processes. There will be, therefore, some overlap associated with those sections and this one, but it is felt that some further mention is necessary herein, in order to include and define any trauma manifesting as a white lesion.

Hirschfeld (1939) stated that when traumatization by the toothbrush results in a blistering of the gingival mucosa, the raised mucous membrane appears as a more or less tenacious, greyish-white, semi-necrotic patch, which is smooth, shiny and may or may not be circumscribed by a bright red line of demarcation. This happens especially when the toothbrush is new (Orban and Wentz, 1960). On the areolar mucosa beyond the alveolar gingivae, or in the fold of the cheek or lip, such a lesion is especially pronounced. It is possible that these lesions can be aggravated by some irritating chemical in the toothpaste. Lesions occur usually on the opposite side, upper or lower, to that hand in which the brush is held. This type of lesion is quite common in the mouths of children (Jacobs, 1956).

It seems to the writer that an automatic electric toothbrush would be less likely to damage oral tissues. McCarthy and Shklar state that this has been proved in experimental animals.

Shira (1957) named tooth brushing, denture irritation, defective

(sharp or rough) restorations, carious sharp teeth or foreign bodies as possible causes of mechanical trauma. He said that there is no uniformity in type of the lesions produced by these various agents and a complete history and careful observations frequently are necessary to arrive at a correct diagnosis. The lesions resolve, he said, on removal of the cause; there is always the threat of malignancy in chronic lesions.

Chewing of the lips and particularly chewing of the cheeks and/or tongue produces a lesion limited usually to one region and consists of an irregular, diffuse outlined area, with a milky white, rough macerated surface. Many patients are often unaware of a habit of tongue or cheek chewing; they usually are "highly strung" types. They will often cease the habit, but it is sometimes difficult to eliminate macerated lesions. These macerated lesions can occur (and the author feels this would be the most common occurrence) in areas where local anaesthesia has been induced, i.e., the lower lip - a grey-white, ulcerated lesion is usually produced (Kerr and Ash, 1960; Miller, 1957; Shira, 1957; Burket, 1961; McCarthy and Shklar, 1964; Shafer et al, 1963).

Long continued trauma, or intense pressure for a shorter time, produces a characteristic reaction often associated with an intact mucous membrane. Habits can cause such lesions, i.e. biting or irritation from ill-fitting dentures and denture bars, the lesion produced usually being of a shape representing the outline of the causative agent, in cases of, say, denture flanges or bars. It is

usually indicated by a white line of necrotic or hypertrophied tissue, or a red, ulcerated area surrounded by white hypertrophic tissue (Bernier, 1955).

Kapur and Shklar (1963) found that the wearing of dentures, which fitted well, seemed to stimulate helpful keratinisation over healthy gums. The areas they used to establish this result (by biopsy) were over the alveolar ridge, whereas in examining the post-dam areas, Ostlund (1958) had found the opposite effect. This latter finding would be a manifestation, though minor, of an over-extended flange where tissue is displaced, which displacement of tissue is found usually in the post-dam area too. Over-extended flanges usually produce, at first, a red, ulcerated area, later surrounded by hyperkeratotic tissue (as stated above), so to this writer, it is not surprising that Ostlund produced the results (of lack of keratinisation) that he did.

Sher (1963) mentioned the ulcerative effect on the mucosa of removing dry cotton wool rolls from the mouth, when they would probably be adherent, due to withdrawal of tissue moisture. The writer has seen cases of whitish lesions produced in these cases, due to a film of necrotic material over the area.

Individuals with thick cheeks that are closely adapted to the buccal surfaces of the teeth can produce what is known as a "linea alba" in the buccal mucosa of the mouth. It is usually initiated by the buccal cusps and is intensified by the habit of sucking and chewing on the cheeks (Colby et al. 1961).

The white traumatic lesion is produced by chronic irritation - the ulcerated lesion may occur from this, but ulceration usually results from more "acute" causes such as a single, or at most a few, traumatic "acts", - i.e. one heavy bite or an ulcer produced by heavy lip biting immediately after local anaesthesia. Ulceration is by far the most common result of mechanical or physical injuries, but the many causes and degrees of ulceration will not be discussed here. However, white patches of necrotic tissue may be associated with ulceration, either directly over the ulcer as slough, or surrounding it, possibly due to interference in the mucosal nutrient supply because of the ulceration.

2. Therapy:

The urgent requirement is to remove any possible cause, either by action or explanation, or both. If a patient suffers from the habit of biting or chewing his cheeks, lips or tongue, Burket suggests the use of chewing gum as a temporary substitute. Hydrogen Peroxide (3 per cent) diluted at least 50 per cent, and slightly warmed, is recommended by McCarthy and Shklar for general cleansing purposes. They feel that infection of lacerated or abraded mucosal areas is not common and routine anti-bacterial medication is contraindicated; the writer agrees. Bernier (1955) suggested antibiotics only if absolutely necessary, and stresses the removal of the cause; ^{and} ~~which~~ in the case of a denture having caused a flap of tissue to develop, the resultant redundant tissue should be removed. Toothbrush injuries can be treated by giving benzocaine lozenges for pain, by cauterizing small lesions with 10 per cent silver nitrate, avoiding hot, spicy foods and further injury and using weak sodium bicarbonate mouth washes (Orban & Wentz, 1960).

B. BURNS

Burns can be divided into four classes, namely:

1. Chemical
2. Thermal (Heat or cold)
3. Electrical
4. Radiation.

1. Chemical Burns:

McCarthy and Shklar divide chemical burns of the oral cavity into those produced by:

- (a) improper use of some medicaments
- (b) the introduction into the mouth of a harsh chemical such as an acid or an alkali; or the use of tobacco, etc.

(a) Aspirin belongs in the first category and every writer on the subject stresses its effect upon the tissue on which it is placed in order to alleviate pain - a white lesion is produced due to necrotic slough which can gradually rub off to leave a red ulcerated area.

This reaction of necrosis is one of coagulation, whereas lye produces a liquefaction necrosis and deep ulceration (Orban and Wentz).

Mouth washes used at high strength may also cause trauma of the aspirin-produced type, such as sodium perborate and hydrogen peroxide, as well as many astringent mouth washes used in periodontal conditions (Bernier, 1955; Glickman and Bibby, 1944; Schroff, 1938).

Toothache drops are a common source of traumatic white lesions (Burket, 1961) producing gingival and mucosal burns.

Sugarman (1952) spoke of the use of chromic acid as contraindicated: newer drugs, although he did not mention any by name, should take its

place. In cases of sloughing following necrosis and ulceration which he saw, sodium bicarbonate was used hourly in warm solution as a mouth wash together with the topical application to the affected part of a 2 per cent aqueous solution of methelyn blue.

Phenol, silver nitrate and trichloroacetic acid are also mentioned in the aetiology of these lesions (Shira, 1957). Aspirin, he said, produces a characteristic thick white membranous lesion which leaves a raw, bleeding surface on removal. Thoma and Goldman (1960) added volatile oils, iodine, copper sulphate and sulphathiazole to the more common medicaments causing lesions (possibly white), together with self-curing resins (in susceptible people) and they also mentioned hydrogen peroxide. Burket states that in some patients a 70 per cent ethyl alcohol solution will result in a sloughing of the mucosa. He stresses that individual reactions to any medicament vary greatly. Aspirin and eugenol are associated with an early painful response.

(b) The use of chewing tobacco, snuff or betel nut cuds is a well-known cause of superficial coagulation or necrosis of the tissues resulting from the irritating properties of the tobacco and/or the "curing" agents and chemicals employed in manufacture. The lesions will only be transitory in nature if the habit is discontinued, but hyperkeratotic changes may result if this action is carried on for any length of time (Burket).

Young children gaining access to dangerous substances is a serious problem. Alkalies such as lysol and lye or strong acids, when accidentally taken by mouth, result in severe and acute trauma to the

oral cavity. Chemicals used by the dentist may cause necrosis, such as silver nitrate, phenol and mercuric chloride. If the burn is caused by silver nitrate or phenol, it is self limiting and pain is relatively slight until sloughing occurs.

This summary of chemical burn aetiology is given by Orban and Wentz (1960):-

Self Medications:

1. Aspirin
2. Silver Nitrate
3. Tincture of iodine
4. Full strength irritating mouth rinses.

Accidental or suicidal use:

1. Lysol
2. Phenol
3. Lye
4. Mercuric Chloride

Accidental Dental application:

1. Phenol
2. Trichloroacetic acid
3. Silver Nitrate, etc.

Occupational:

1. Acid fumes.

2. Thermal Burns:

Hot instruments cause necrosis if applied to or allowed to touch mucous membrane, much the same lesion being produced as is caused by phenol (Shira, 1957). They are easy to recognise.

Bernier (1955) feels these traumas are usually brought about by hot foods or liquids. Both McCarthy and Shklar, and Burket mention pizzas as a very common cause of oral burns, with the palate, tongue and lips the areas most frequently affected. Bernier feels that burns

start as vesicles. The lesions of excessive cold, such as dry ice or refrigeration anaesthetics, begin, however, as white, irregular patches, because of initial necrosis, but soon disappear to reveal a red painful ulcer.

3. Electrical Burns.

Electrical burns from appliances or wires are out of the scope of this paper. The damage can be enormous.

Galvanic production of lesions (hyperkeratoses) was discussed under "Abnormalities of Epithelial Components".

4. Radiation Burns.

During the course of radiation therapy for malignant oral or head lesions, the oral mucosa may react according to its own particular resistance or to the mode of delivery, the type of radiation and the size of the area radiated.

The early mucosal reactions are described as, firstly, erythematosis, leading to areas of desquamation and after about 10 days or longer, the entire mucosal surface may be denuded of epithelium and covered with a whitish-grey membrane. Healing can be very slow, complicated by secondary infection. The late stages are characterised by very thin, delicate mucous membrane which is easily traumatised. This mucous membrane is usually devoid of rete pegs and the corium presents collagen degeneration with fibrosis of vascular channels (Burket, 1961; Shafer et al, 1963; McCarthy and Shklar, 1964).

Diagnosis of burns: can usually be made on the basis of history of development, duration, appearance and physical characteristics of

the affected tissues. The coagulum can usually be removed fairly easily. Moniliasis, oral hyperkeratoses and lichen planus must be considered in the differential diagnosis. The lesions associated with syphilis should not present differentiation problems (Burket). Orban and Wentz include erythema multiforme and bullous lichen planus, as it is doubtless felt that blisters and ulcers would occur in many multiple burn sites.

Therapy of Burns: Treatment of burns of the oral mucosa is usually symptomatic, due to the fact that the patient has not been seen immediately, due to obvious circumstances, so that it is usually too late to advise the neutralisation or dilution of an acid, for instance (Burket).

If pain is severe, codeine or other narcotic is required. The area should be cleansed and covered by an adherent paste containing a cortico-steroid such as triamcinolone (Orabase, the adherent paste, has been mentioned in a previous chapter).

In radiation burns, combinations of steroids and antibiotics in ointments may be helpful. Systemic cortico-steroids should be used in severe cases (McCarthy and Shklar, 1964).

Accidental phenol burns should be treated immediately with 70 per cent alcohol. Again, sodium bicarbonate, 1 teaspoonful in a glass of warm water is mild and soothing, together with some form of topical anaesthetic. Karo syrup in water to coat sore areas and the use of hydrocortisone acetate (2.5 per cent) topically applied is recommended by Orban and Wentz, provided the cortisone is used for a few days only.

Schulz and Vazerani (1961) suggested a nembutal suppository of from $\frac{1}{2}$ to 1 grain in the case of an infant; for a child, one aspirin; for an adult $\frac{1}{4}$ grain of morphine. If necessary, a bland liquid diet is best taken through a glass straw, - this would aid in preventing further trauma from food.

Meyer and Shklar (1957) summed up the above treatments and suggestions in an excellent article; they condemned the local use of antibiotics, - with which the writer agrees.

Histopathology for all Trauma:

If the histopathological appearance is required in order to rule out dyskeratosis in cases of long-standing traumatic lesions, hyperplasia of the covering epithelium (if intact) would be seen, elongated rete pegs usually being present. The corium is often infiltrated by chronic inflammatory cells, such as lymphocytes and plasma cells.

If ulceration is present, a pyogenic membrane forms early, to be replaced by necrotic tissue. In such circumstances, the epithelial covering, of course, would be absent. In the pyogenic membrane composed of fibrin and necrotising material are leucocytes and desquamated cells. Of importance, is the change often noted at the edge of the laceration (or burn); here, extreme mitotic activity and morphologic alteration of the cells occur, often leading to a mistaken diagnosis of malignancy (Bernier, 1955; McCarthy and Shklar, 1964).

SECTION 4.

VERRUCA-LIKE LESIONS AND LESIONS
OF A PAPILLOMATOUS NATURE

- A. PAPILLOMA
- B. PAPILLOMATOSIS AND INFLAMMATORY PAPILLARY
HYPERPLASIA
- C. SOME BENIGN TUMOURS OFTEN TERMED "PAPILLOMAS"
- D. THE WART
- E. MOLLUSCUM CONTAGIOSUM
- F. MOLLUSCUM PSEUDOCARCINOMATOSUM (KERATOACANTHOMA)
- G. VERRUCOUS CARCINOMA.

VERRUCA-LIKE LESIONS AND LESIONS OF A PAPILLOMATOUS NATURE

INTRODUCTION

The lesions encompassed by this grouping are few in number, but vary between complete benignity (even if only temporary) and malignancy.

Clinically, the single lesions of the group may not differ greatly in appearance, for they have been included for the very reason that they are similar, but from a histopathologic, and possibly aetiologic, viewpoint, they are entities and will be considered as such in this chapter.

A. THE PAPILLOMA

1. General.

Cheraskin and Langley (1956) said that the word "papilloma" derives from "papilla-" (nipple) and "-oma" (tumour).

The papilloma is described by Thoma and Goldman (1960), Scopp and Frederics (1961), Shafer, Hine and Levy (1963), McCarthy and Shklar (1964) and Cook (1951), indeed most writers, as a benign tumour of the epithelium. Papillomas occur either as soft outgrowths from the surface of the mucous membrane, or as hard hornified "warts" in areas of epithelium affected by progressive keratosis: they may be single or multiple. Thoma and Goldman stated that papillomas are potentially malignant, which statement is reiterated by Bernier (1955), McCarthy and Shklar, (1964), Shafer et al, Castigliano (1961), Halperin (1957), Cheraskin and Langley (1956).

Bhaskar (1960) and Mead (1940) on the other hand, stated that oral papillomas do not undergo malignant change and Gorlin (1957) had never seen an authenticated case of malignancy in a papilloma.

Gorlin felt that there is confusion of this benign lesion with the verrucous or exophytic squamous cell carcinoma, which, in the opinion of the author of this review, would be almost impossible to disprove.

Mead (1940) said that papillomas tend to grow outward instead of inward and never break through the limiting basement membrane. However, he added that if they recur after removal, malignant tendencies should be expected, which this author feels is somewhat contradictory to the statement he had previously made.

Rushton and Cooke (1959) said that highly keratinised papillomas may be associated with a patch of hyperkeratosis, a condition which this author has seen on the tongue. They consider the papilloma to be potentially pre-cancerous, especially with the aforementioned association and Archer (1957), too, felt that these lesions of the tongue, and cheeks as well, which have a fixed base and induration of the underlying tissues, should especially be regarded with suspicion.

Thoma and Goldman (1960) quoted Ewing, who stated that a gradual transformation from benignity to malignancy has been fully demonstrated in a papilloma. It is felt that unless the biopsies were taken in different areas initially, a false negative result may have been found, leading to a wrong inference. However, Thoma and Goldman stated that true papillomas (squamous) are definitely at least neoplastic, the soft type being generally pedunculated, but at times sessile, a flabby sessile type adapting itself to conditions of mastication and generally giving no trouble; the hard type of papilloma forming a horn-like projection, or a mass of folds if cauliflower-shaped, but they warned of the danger of fixation of the base and surrounding induration.

Stones (1962) associated the hard type usually with adults, where it often occurs with hyperkeratosis and an aetiology of irritation. The colour, of course, would depend on the amount of keratinisation (McCarthy and Shklar). Mead described the hard type as being white, while the soft ones were red or greyish, cauliflower-like growths.

In 1939, Prinz and Greenbaum outlined how the term "papilloma" is used in both a clinical and a pathologic sense. The term, they said, has been used clinically to describe all sorts of elevations in the mouth, pedunculated and sessile, under which conditions the term merely signifies an elementary or primary lesion, somewhat in the same sense as the terms vesicle, papule, etc. are employed. In the mouth, Prinz and Greenbaum observed both infectious and traumatic papillomas and these are difficult to differentiate clinically: the infectious type they described as the ordinary wart, which did not resemble its skin manifestation. Both types do not necessarily presage malignant change. They were described as painless, smooth, firm or soft, pin-head size to much larger hemispherical elevations, often pedunculated. The two types, infectious or traumatic, could disappear spontaneously, but the latter may become malignant; the infectious papillomas or warts are usually softer than the traumatic types and are often associated with warts of other parts of the body, a fact which can be of great diagnostic value. This latter statement was reiterated by McCarthy and Shklar (1964).

Toto (1957) felt that the so-called verruca vulgaris of the oral cavity is really another type of papilloma; Shafer et al also stated

that a virus aetiology has never been proven as a cause of human oral papilloma and that no papilloma in a human has been induced by injection of cell free extract of an oral papilloma from another person, although multiple oral papillomas do occur. Colby et al (1961) noted that children can have multiple lesions, which, until the age of puberty, tend to recur after removal. Could puberty initiate some tissue resistance or even a change in oral environment preventing virus proliferation?

As Prinz and Greenbaum had said earlier, "papilloma" is a much abused category for oral lesions. Any raised peduncular lesion in the oral cavity is likely to be called a papilloma. Fibromas and myxofibromas are often designated as papillomas by the clinician: many "growths" of this type do not appear as definitely encapsulated masses and there is serious doubt about their always being true neoplasms (Boyle, 1954).

Thoma and Goldman described papillomas as very small to 2 or 3 cms. in diameter and this is universally agreed upon. McCarthy and Shklar say that the general overall appearance varies, being governed by the number of projections from the surface, the relative thickness of these projections (some may be filiform) and the amount of keratinisation.

Shafer et al stated that papillomas are frequently confused with fibromas, but they felt that there should be no difficulty in distinguishing between them clinically since each has certain definite characteristics. They described the papilloma as an exophytic growth

made up of numerous, small, finger-like projections which result in a lesion with a roughened, verrucous or cauliflower-like surface. It is nearly always a well circumscribed pedunculated tumour, occasionally sessile. It is found intra-orally, usually on the tongue, lips, buccal mucosa, gingiva and palate, particularly that area adjacent to the uvula. However, no predilection of site is given. A case has even been reported occurring in the duct of a mucous gland (Castigliano and Gold, 1954).

Thoma and Goldman, naming the same sites of occurrence as Shafer et al, warned that the foliate papillae on the posterior margins of the tongue should not be confused with a neoplasm. Stones (1962) and Cheraskin and Langley (1951) also gave the same sites, but the latter felt there is a definite predilection for the uvula area. Bernick (1948) found papillomas on the gingivae and palate with the majority occurring on the palate and presenting an irregular surface which, on probing, seemed to be composed of multiple, small projections. Archer (1957) and Bhaskar (1961) noted their presence on the hard palate, lips and tongue. Archer felt that the soft papilloma is usually pedunculated and can be flattened by a covering prosthesis; Bhaskar, that usually intra-oral lesions were soft, while those on the lips were usually rough and scaly. Bernier (1957) gave the usual lip site as just inside the mouth. McCarthy and Shklar gave the occurrence site as the tongue dorsum and buccal mucosa; Prinz and Greenbaum (1939), the tongue usually, but anywhere in the oral cavity.

Bernick (1948), Bhaskar (1961), McCarthy and Shklar (1964),

Shafer et al (1963) - in fact most authors, agree that "true" papilloma can occur at any age in either sex and that the lesions may be single or multiple. However, Bernick, as well as Cheraskin and Langley, have found that approximately three-quarters occur during the 5th and 6th decades, Cheraskin and Langley finding that trauma to the lesions, leading to ulceration and haemorrhage, would be the chief complaint when a patient is seeking therapy for the condition. They also stressed the necessity of biopsy in diagnosis.

Stones said that true papilloma is a relatively uncommon tumour in the mouth. The author feels that the use of the term "papilloma" to describe all sorts of oral excrescences and pedunculated out-growths is to be condemned. Apparently other neoplasms and/or hyperplasias have all, at times, been grouped together clinically under one heading, - "papilloma"; in this grouping have been included, fibroma, fibro-epithelioma, myxo-fibroma, lipo-fibroma, or osteo-fibroma, and hyperplasias such as epulis granulomatosa, inflammatory papillary hyperplasia, epulis fissuratum and polyps, not to mention warts (if they are separate oral entities), kerato-acanthoma and malignant carcinomas.

McCarthy and Shklar have reported an inward growing papilloma rather than the usual exophytic growth, although they maintained that the condition is quite unusual. Cahn in 1941 spoke of one variety of papilloma in which the keratinised prolongations of epithelium, instead of rising above the surface, appeared to dip downwards and curl upon themselves; he found this type of papilloma mostly in the mouths

of heavy smokers. Moskow and Moskow(1962) also reported a similar endophytic type occurring on an edentulous mandibular ridge as a pearly white lesion. It was rough to palpation and appeared to contain minute surface crevices. The adjacent surface tissue was ulcerated irregularly, and inflamed. They stated it was only the second one reported in thirty years.

2. Histopathology

The Soft Papilloma is composed almost completely of epithelium, but for a pedicle of connective tissue containing nutrient vessels and nerves (Thoma and Goldman). Through the tumour run thin connective tissue cores, which are covered by stratified squamous epithelium, with or without inflammatory infiltrate either due to irritation or to local infection (Bernick). McCarthy and Shklar said that the individual folds of the exophytic lesion tend to widen as they stretch outward from the central area of the lesion and the outer epithelial surface is well keratinised, being responsible for the white appearance. They feel the connective tissue core may be highly vascular. There may be areas of dyskeratosis.

Hard Papillomas have a thick covering of keratin over epithelium which is so folded as to produce a wart-like appearance. Shafer et al stated that the essential feature of all papillomas is a proliferation of the spinous cells in a papillary pattern: the connective tissue present is only supportive and not considered a part of the neoplastic element.

The Fibropapilloma exhibits hyperkeratosis and acanthosis of the epithelium with the fibrous connective tissue being very prominent. The tumour is usually pedunculated and a wider pedicle is seen with quite expansive growth (Thoma and Goldman). (The fibrous tissue is not neoplastic, only hyperplastic, as previously stated).

Toto (1957) stated that "it is significant that, although the papilloma may be quite large, it requires only a moderate blood supply to nourish its cells. This is an index of the benign nature of the tumour".

The author does not agree that lack of blood supply has been proven to be an indication of benignity. In any case, most writers on the histopathology of the papilloma (true) feel that the connective tissue core is prominently vascularised.

3. Aetiology (Papilloma)

Tiecke (1957) stated that trauma, infection, metabolic disturbance and viral origin have been implicated in the aetiology. Bernick (1949) said that it has not been determined whether papillomas are true neoplasms or a simple response of the epithelium to chronic irritation. He felt that the usual course of papillomas is benign, with limited growth capacity.

Mead (1940) said the papilloma may be caused by proliferation of embryonic or misplaced cells.

Stanley et al (1964) described the production and histopathology of tumours appearing in oral, dental and related tissues of mice inoculated at birth with polyoma virus (parotid tumour agent), some of which tumours arose from gingival epithelium. They presented 3 stages

of differentiation:-

1. Basal type cells, closely packed together and quite basophilic.
2. Cells with more abundant cytoplasm and prickly formation: nuclei less basophilic.
3. Cells forming keratin in a variety of patterns.

It seems to the author that further work on this subject could be done. A control group, where normal parotid tissue was used, would be advantageous.

4. Diagnosis

Bradley (1944) declared that careful examination is necessary of any apparent neoplasm to determine its physical characteristics. A biopsy is important and this has been advocated in all articles concerning papilloma read by this reviewer.

Bradley suggested the following plan for a study in diagnosis:-

1. The history of the tumour - (time of appearance)
2. The precise location
3. The rate of growth (author: important)
4. The tissues involved
5. The possibility of trauma as an exciting factor
6. The condition of nearby teeth
7. Pain, discomfort, disfigurement
8. Glandular involvement (lymph nodes)
9. Evidence of any general systemic disease.

This, with biopsy, would be used in differential diagnosis of true papilloma and the other conditions described at times as "papillomas".