

Stomatitis Nicotina.

Leukoplakial lesions occurring on the hard palate present certain distinct clinical features. Thoma (1941), Kerr, Saunders (quoted by Waldron and Shafer, 1960), Bernier (1959), Cheraskin and Langley (1956), Bhaskar (1961) all regard this as a distinct clinical entity, calling it "stomatitis nicotina", or "smoker's palate". Waldron and Shafer quote Cummer, Ward and Cooke as disagreeing, while Cahn (1941) disputed the claim that the red spots in this condition are due to the orifices of the palatal glands, but simply to an atypical form of leukoplakia.

The lesion is described by Orban and Wentz (1960), Burket (1961), Stones (1962); (but not called stomatitis nicotina) and Shafer, Hine and Levy (1963).

The clinical appearance seems to be described uniformly by most authors. It is first manifested by redness and inflammation. Soon the palate develops a diffuse, greyish-white, thickened, multinodular or papular appearance, with a small red spot in the centre of each tiny nodule, representing the dilated and sometimes partially occluded orifice of an accessory palatal salivary gland duct. Fissures and cracks may appear, producing a wrinkled, irregular surface.

Cheraskin and Langley state that the most profound changes occur in people with fair skin and hair, but Bernier does not agree.

Histopathology.

Various authors have described the histopathology of leukoplakia.

Hobaek (1946); Epithelial hyperplasia with hyperkeratosis, acanthosis, and chronic inflammatory infiltration in the corium, usually of plasma cells and lymphocytes, sometimes polymorphs. An increase in the number of mitoses was the first sign of transition to malignancy. Then came loosening of cellular borders, and breaking through of the basal cell layer.

Sharp (1948); Similar to the formation of calluses on the hands of manual labourers. The white portion is due to layers of keratotic, dead epithelium, heaped over an abnormally thickened stratified squamous epithelium.

Cheraskin and Langley (1956); Parakeratosis, hyperkeratosis, acanthosis - hyperplasia in the stratum malpighii, and occasionally hydropic degeneration are seen. Chronic inflammatory cells in the superficial layers of the corium are a fairly constant finding. As leukoplakia is a progressive condition, so the clinicopathologic picture is quite variable.

Cahn (in Russ, 1957); On a histological basis, two entities seen, the distinguishing factor being a well marked, horny layer, called keratosis, the first category. Transition from keratosis to marked epithelial hyperplasia will be seen,

with loss of the hornified zone, and great increase in size of the prickle cell zone. This type of transformation is a malignant trend on the part of the tissues.

Kollar et al (1954); presented a classification for maturation disorders of the epithelium:- (1) Hyperplasia, (2) Hyperkeratosis and inflammation, (4) Hyperkeratosis, dyskeratosis and inflammation, (5) Intraepithelial cancer, (6) Epidermoid Carcinoma.

Sharp et al (1956); One or all of the precancerous microscopic changes (acanthosis, parakeratosis, hyperkeratosis, dyskeratosis) are present and are associated with varying degrees of inflammation, usually of a chronic nature.

Renstrup (1958); Of 90 cases, hyperkeratosis and parakeratosis were present in 71 cases, generally co-existing. Epithelial hyperplasia was present in 24 patients, - defined as an increase in the number of cells in the prickle cell layer. Degenerative changes were present in the epithelium in five cases in the form of intra- or intercellular oedema of the Malpighiian layer. There were two cases of dyskaryosis - hyperchromatism, variation in nuclear size and shape, abnormal, premature and imperfect keratinization. In ten cases there were multi-nucleated cells in the prickle cell layer, there being 10 - 12 nuclei in the same cell. In extreme cases "pre-keratin bodies" may occur in the prickle cell layer. They appear as eosinophilic areas in the

cytoplasm, and with regard to morphology and staining quality, they are quite different from the keratohyalin granules of the granular layer. Lymphocytic and plasma cell infiltration of varying degrees of severity was found in the connective tissue in 42 cases, and fibrosis in 5 cases.

Fasske et al (1959); 103 patients were divided into four groups, according to the histologic picture; (1) Uncomplicated epithelial hyperplasia, (2) Surface keratosis, hyperkeratosis or parakeratosis, (3) Hyperplasia and keratosis, (4) Atypical epithelial changes. Using the electron microscope, these workers found that the basal cells of leukoplakia showed a large number of mitochondria and a lamellar structure, but few tonofibrils within the cytoplasm. (This may be compared with the findings of Zelickson for normal keratinizing epidermis, as he found numerous tonofibrils). During cornification, they found an increase in the number of tonofibrils, and decrease in the number of mitochondria, and keratohyalin granules were formed.

Bernier (1959); For "pachyderma oris" - hyperplasia, sometimes with broad fused rete pegs extending deeply into the corium, or there may be minimal increase in thickness. Oedema is usually seen, and if keratosis is marked, the stratum granulosum is often prominent. There may be chronic inflammation in the corium.

For "leukoplakia" - hyperplasia, broad and elongated rete pegs, the granular layer may be prominent, spongiosis of the Malpighian layer may also occur, particularly in early lesions. Usually either hyperkeratosis or parakeratosis is present. A chronic inflammatory exudate (lymphocytes, plasma cells and sometimes macrophages) is usually present close to the basal layer. Dyskeratosis is present, and its importance is emphasized by Bernier, who deprecates the use of the term carcinoma-in-situ, since without invasion, it is difficult to assume malignancy.

Thoma and Goldman (1960); Follow the description of Bernier.

Orban and Wentz (1960); For hyperkeratosis simplex - a thickening of the keratin and granular layers of epithelium; no other epithelial change; no inflammation in the corium.

For hyperkeratosis complex - an increase in thickness of keratin and granular layers; acanthosis and thickening of the epithelium; widening of the basal cell layer with increased mitotic activity; dyskeratosis evident as keratinization of single cells of prickly cell layer; and hyperchromatic nuclei of the epithelial cells. The basement membrane is intact, and the connective tissue shows a lymphocytic and plasma cell infiltration.

Shafer and Waldron (1961); 85% of 332 specimens consisted of benign and innocuous lesions characterized by hyperkeratosis and acanthosis, parakeratosis and acanthosis, hyperkeratosis and parakeratosis together, or hyperkeratosis alone. A few lesions showed only acanthosis or only parakeratosis. It was of interest that parakeratosis alone was relatively uncommon in contrast to hyperkeratosis alone, whereas parakeratosis in association with acanthosis was seen more frequently than hyperkeratosis with acanthosis.

There appeared to be no real differences in the occurrence of the different forms of epithelial dysplasia between men and women, except for the greater preponderance of carcinoma in men, a well recognized clinical phenomenon.

In 26 cases, (7.8%) focal atypia was present. Six cases of carcinoma -in-situ (extreme dyskeratosis), and 27 cases of invasive carcinoma, all clinically diagnosed as leukoplakia, were found. These three categories represented 17.7% of all white lesions biopsied (excluding lichen planus and all other specific entities).

Shafer and Waldron; gave the following histologic interpretation of

332 white lesions:-	<u>per cent</u>
Hyperkeratosis without acanthosis	26.2
Parakeratosis without acanthosis	5.4
Acanthosis only	1.8
Hyperkeratosis with acanthosis	25.6
Parakeratosis with acanthosis	31.6

	<u>per cent</u>
Hyperkeratosis, parakeratosis, acanthosis	
with focal atypia	7.8
Carcinoma in situ	1.8
Carcinoma invasive	8.1
Leukoedema with or without hyperkeratosis, parakeratosis or acanthosis	9.0

Bhaskar (1961); Follows the description of Bernier

Chomet et al (1962); Suggest that proliferative and neoplastic changes
be classified as follows:-

1. Hyperplasia.
2. Leukoplakia, meaning hyperplasia, hyper- or parakeratosis
and inflammation.
3. Dysplasia.
4. Carcinoma in situ.
5. Early invasive carcinoma.
6. Carcinoma.

Hyperplasia and leukoplakia are proliferative phenomena of
the epithelium, basically without maturation disorders.

The epithelium may expand exophytically and endophytically,
maintaining its usual pattern and arrangement.

The dysplasia often shows attenuation of the epithelial
layer, developing in a thick leukoplakic epithelium. The
dysplasia shows partial dedifferentiation of the epithelium,
frequently involving only the deep layers. The nuclei are
crowded, without loss of nuclear polarity, large, and
sometimes show a perpendicular arrangement. The nucleoli

are uniformly prominent, while the cytoplasm shows no coarse chromatin. Only slight mitotic activity is noted.

Carcinoma in situ shows total or partial dedifferentiation of the epithelium. In cases of partial dedifferentiation, only the deep portion of the epithelial layer may be involved. The cells are crowded with varying loss of nuclear polarity. The nuclei are pleomorphic and hyperchromatic. Atypical mitotic activity is noted. The basement membrane of the epithelial layer is fully preserved.

Stones (1962); Any of the following histological changes may be seen; hyperplasia, hyperkeratosis, parakeratosis, dyskeratosis, intra-epidermal carcinoma or squamous cell carcinoma, together with varying degrees of sub-epithelial inflammatory infiltration. Hyperkeratosis is seen in the well established lesions, with a thick keratin layer and a well marked granular layer. In parakeratosis, there is absence of the granular layer and nuclei are present in the superficial epithelial cells. There is marked acanthosis with deepening of the epithelial ridges overlying a dense infiltration of inflammatory cells, which are mainly lymphocytes and plasma cells. It is often difficult to determine precancerous changes in the lesion, but these may be indicated by dyskeratosis with atypical or premature keratinization of individual cells, hyperchromatism,

changes in polarity of nuclei in the basal cells; increase in mitotic figures, and often a markedly irregular acanthosis.

Rushton and Cooke (1963); The early lesion - occurring on non-keratinized mucosa, may show either parakeratosis or keratosis. Those occurring on keratinized mucosa show hyperkeratosis. There is variable acanthosis, a mild lymphocytic infiltration, and capillary dilation in the corium. With removal of the irritant, the condition may be reversible over a period of time.

The established lesion - (1) A thick keratin and well marked granular layer; (2) Acanthosis with deepening, broadening and sometimes forking of the epithelial ridges; (3) Although mitotic figures are seen, there is no pleomorphism of the prickle or basal cells; (4) There is often a well-defined eosinophilic condensation of the corium adjacent to the basal cells; (5) Diffuse lymphocytic and plasma cell infiltration of the corium.

The late lesion - In the stage of transition from hyperplasia to neoplasia; (1) The keratin layer varies in thickness due to desquamation; (2) Acanthosis is more marked, with irregular downgrowth of the epithelial ridges; (3) Mitotic figures are frequent and there is individual cell dyskeratosis and clumping of nuclei; (4) Many prickle cells are vacuolated, and there is loss of polarity of the basal

layer; (5) Many of the epithelial cells are hyperchromatic; (6) There is a very dense lymphocytic and plasma cell infiltration which reaches and invades the basal layer with disruption of the latter; (7) There is degeneration of the elastic fibres, and sometimes of the collagen fibres in the infected area.

All gradations are seen between the above findings and a frank carcinoma with atypical mitotic figures, multinucleated cells, epithelial cell nests, and malignant infiltration.

Hellinger et al (1963); Tabulated their histologic findings under five major headings:-

1. Hyperkeratosis.
2. Keratosis and acanthosis.
3. Dysplasia ("leukoplakia"). In addition to the foregoing, there was a significant loss of polarity in the mucosal lining, with distinct but limited areas of uniform maturation. These atypical areas were characterized by cells exhibiting hyperchromatic nuclei, pleomorphism, and increased mitotic activity.

Dyskeratosis might be present. A marked subepithelial inflammatory cell infiltrate was usually present.

4. Carcinoma-in-situ.
5. Invasive carcinoma.

Shafer, Hine and Levy (1963); Recapitulate the findings of Shafer and Waldron (1961).

Shira (1964); Follows Bernier's classification of white lesions into pachyderma oris and leukoplakia.

McCarthy and Shklar (1964); The microscopic picture of leukoplakia tends to show one of the following conditions:-

Simple hyperkeratosis; There is an increased width of the stratum corneum, appearing as either a hyperkeratosis or a parakeratosis. With the hyperkeratosis, there may be an accentuation of the stratum granulosum. Acanthosis and some extension of rete pegs may be apparent, particularly in lesions of the alveolar mucosa and tongue. Chronic inflammatory infiltration into the underlying connective tissue is minimal or absent. This type of lesion represents a simple keratotic response to some mild irritant or stimulant.

Hyperkeratosis and Inflammation; Here there is hyperkeratosis and often notable inflammatory infiltration into the underlying connective tissue, consisting of lymphocytes, plasma cells, histiocytes, and scattered polymorphs. Dilated capillaries are often in evidence. There may be extension of rete pegs, and some hydropic degeneration may be seen in the stratum spinosum.

The degree of keratinization is variable. The stratum corneum may be as thick or thicker than the rest of the epithelium. The thickness of the keratin layer can be correlated with the white opacity and the raised appearance of the clinical lesion.

Hyperkeratosis and Dyskeratosis; In addition to a hyperkeratosis there is evidence of dyskeratosis or an abnormal orientation of the epithelium with cellular atypism. The width of the stratum corneum may be very great, or it may be minimal. The notable alterations are seen in the stratum germinativum and the stratum spinosum. There is a lack of cohesion between epithelial cells, and the tonofibrils appear well defined as the cells separate. The clear demarcation between the different zones is absent, and the deeper staining nuclei of the basal layer are no longer outlined. Large bizarre cell forms are in evidence. The nuclear : cytoplasmic ratio appears altered, and increased mitotic activity may be noted. The connective tissue is infiltrated with chronic inflammatory cells, and there is not the usual clear separation between epithelium and connective tissue at the basement membrane zone. The epithelium and connective tissue appear to blend into one another. However, there is no obvious invasion of the epithelium into connective tissue. This type of leukoplakic reaction will eventually give rise to a frank epidermoid carcinoma, and is to be considered a definite premalignant lesion or a carcinoma in situ.

Feagans and Burke (1964); Studied the fine structures of hyperkeratotic changes. As compared to normal oral non-keratinizing variety, the most conspicuous changes were

observed in the amount of cytoplasmic fibrillar material, and the presence of relatively large numbers of mitochondria continuing into the more superficial layers.

A well-developed stratum granulosum was present several cell layers thick, containing prominent granules of keratohyalin which increase from submicroscopic size in the upper spinous layer to large irregularly shaped masses of electron-dense granules in the few layers just beneath the stratum corneum. The change from the stratum granulosum is abrupt without an intervening transitional cell zone, as is described in some cases of normal keratinizing epithelium.

The Histopathology of Stomatitis Nicotina.

These lesions show the same range of variation in the epithelium as described above, together with specific reactions due to the anatomy of the area. The connective tissue under the epithelium, around the salivary gland ducts, and in the interstitial tissue of the palatal salivary glands, shows oedema and plasma cell and lymphocytic infiltration. The ducts of the salivary glands show intraductal epithelial proliferation and plugging of the lumina. The plugging and inflammatory exudate produce the characteristic "bumps" and the hyperkeratinization produces the characteristic white appearance of this lesion. Except for an early difference of opinion by Cahn (1941), most authors seem to be agreed on the histopathology of "stomatitis nicotina", but many do not consider that it warrants classification as a separate entity. This reviewer feels that it is not necessary to treat it as a separate entity, as the condition is

similar to leukoplakia elsewhere in the mouth, but modified by the specific anatomy of the area.

Conclusion.

In scanning the above review of the histopathology of leukoplakia, it is obvious that the histopathology of these white lesions is fully as varied as the clinical appearance. There is a natural, and praise-worthy, attempt on the part of the pathologist to simplify and sort out this picture so that a specific description can be conveyed to the clinician, in order to give him a clear indication of what line of treatment to pursue. In making this attempt, terms have been used to embrace a number of changes and, inevitably, inaccuracies arise. One example has already been pointed out - in the case of "dyskeratosis"; this term may have appeared adequate when introduced more than 20 years ago, but since the advent of the electron microscope, it seems inaccurate and misleading. This reviewer thinks that the only course to be followed is for the pathologist to describe sections in clear and simple words in detail, avoiding the use of "shotgun" terms, and for clinicians to provide themselves with a sufficiently broad knowledge of pathology to be able to interpret these correctly. For this reason, the treatment by Rushton and Cooke of the histopathology of white lesions appeals tremendously. The three stages - early, established and late lesions are described in clear and unequivocal terms, with the final qualification that "all gradations are seen between the above findings and a frank carcinoma, etc."

Histochemistry.

Fasske et al (1959) found that, in leukoplakia, the basal cells decompose the glycogen present under an aerobic condition, but the epithelial cells contain glycogen deposits which are later used as energy for differentiation processes. They found also that, during cornification, keratohyalin is formed, resembling the material of the stratum granulosum of the epidermis, while at this stage the glycogen disappears, and the stored saccharides are used up. Fasske et al thought that this process is promoted by the adenosine triphosphate and phosphatase of the cell nuclei. (Note that Zelickson found that acid phosphatase activity has been associated with the lysosomes of the cytoplasm, not with the nucleus.)

Turesky et al (1961), using the Barnett-Seligman technique, found significant differences between the hyperkeratotic and parakeratotic lesions. It was demonstrated that in hyperkeratosis there was a well-defined transitional zone between the keratohyalin layer and the stratum corneum which was not present in parakeratosis. This zone has been described in the literature as a feature of so-called "hard" keratinization which occurs in such structures as nails or hair. Hyperkeratotic and parakeratotic lesions also differed in the distribution of sulphhydryls and disulphides. In hyperkeratosis, the sulphhydryl content was greatest in the well-defined transitional zone. In the stratum corneum the sulphhydryl content was notably reduced in comparison with the transitional zone, and was even less in the Malpighian layer. In parakeratosis in

which there was no well-defined transitional zone, the greatest concentration of sulphhydryl occurred in the stratum corneum.

The distribution of disulphide groups added meaning to the difference in sulphhydryl content of the hyperkeratotic and parakeratotic lesions. Disulphide was increased in the hyperkeratotic lesions where the sulphhydryl content was reduced in the stratum corneum. In the parakeratotic lesions where sulphhydryls were increased in the stratum corneum, the disulphide content was negligible. It would appear then, that a major difference between hyperkeratotic and parakeratotic lesions lies in the degree of oxidation of sulphhydryls to disulphides. As previously mentioned, Droust and Haruko Amano stated that decreased deoxyribonuclease activity of the keratogenous zone is associated with retention of nuclei in parakeratotic areas. It is quite likely that the two preceding statements are complementary, and not conflicting, although the complete picture is difficult to visualize.

Turesky et al found that glycogen in the epithelium, interpreted as indicative of cellular activity, was generally confined to the parakeratotic lesions.

Cahn et al (1961 & 1962) in a study of 100 white lesions, found them to be distributed as follows:-

Epithelial hyperplasia	7
Epithelial hyperplasia with keratosis	35
Epithelial hyperplasia with parakeratosis	40
Epithelial hyperplasia with dyskeratosis	1

Lichen planus	9
Discoid lupus	2
White naevus	6

In these 100 lesions, when stained with pa - S stain, it was possible to demonstrate the basement membrane in each case. In several instances of disorientation, the basement membrane stained brightly and was intact. On the other hand, in some instances of disorientation and dyskeratosis, the basement membrane was vague and appeared to be undergoing dissolution. In one case of epithelial hyperplasia with a lichenoid infiltration, the membrane was vague and interrupted, and in this case, neoplastic changes later developed.

These findings concerning the basement membrane led Cahn et al to the tentative conclusion that there is a substance, possibly enzymatic in nature, elaborated by malignant epithelial cells, that dissolves the pa - S positive material in the basement membrane. This same substance may be present in the potentially malignant cells, such as are found in areas of disorientation without invasion, (leukoplakia, intraepithelial carcinoma, etc.). Furthermore, Cahn et al tentatively concluded that the pa - S stain may make it possible to distinguish potentially malignant epithelium and maybe to separate benign white lesions from potentially malignant ones.

Jolly (1964), in his study of vitamin A deficient rats, found the basement membrane is disrupted. Abnormally pale and irregular staining with pa - S stain indicates alteration in the glycoprotein portion of the basement membrane. It is interesting that Cahn et al did not relate disruption of the basement membrane to vitamin A deficiency.

In analysing the glycogen content of white lesions, Cahn et al found that none of the 34 hyperkeratotic lesions showed glycogen in the epithelium, whereas glycogen was found in the epithelium of 41 of 52 parakeratotic lesions. The correlation between parakeratin and glycogen in an inverse relation of keratin and glycogen has been demonstrated in normal epithelium. As the Table below indicates, this relationship is essentially unchanged when keratin and parakeratin are produced in such abnormal amounts as to produce clinically white lesions.

Type of lesion	Glycogen positive	Glycogen negative
Keratotic	0 (%)	34 (100%)
Parakeratotic	41 (79%)	11 (21%)

In all cases in which glycogen was present, it was found to be concentrated in the middle and outer layers of the epithelium. The basal portion of the epithelium was consistently found to be free of glycogen. Additional studies under way with methyl-green pyronine stain showed a marked increase in ribonucleic acid in the glycogen-negative area. This seems to be in harmony with the work of Droust and Haruko Amano who showed that nucleic acids, present in lower levels of the epithelium, rapidly disappear at the upper limit of the Malpighian layer under the influence of the nucleases, and that disturbances in nuclease activity or distribution may likely result in abnormal keratinization.

In Cahn et al's study, 11 out of 52 parakeratotic lesions were glycogen free. Analysis revealed that all of these cases

exhibited, in sections stained with haematoxylin and eosin, morphologic and staining characteristics which are usually considered suspect. In 2 of the cases, frank carcinoma subsequently developed. By comparison, examination of the 41 parakeratotic lesions which did contain glycogen showed only 2 with a malignant potential.

Type of lesion	No. of Cases	No. with Malignant Potential
Parakeratotic with glycogen	41	2
Parakeratotic without glycogen	11	11
Keratotic with glycogen	0	0
Keratotic without glycogen	34	0

Subject to the analysis of additional cases, Cahn et al tentatively suggested that this condition, parakeratosis without glycogen, may be a sinister sign in the prognosis of white lesions of the mouth.

Porter and Flanagan (1963) studied the glycogen distribution in papillary hyperplasia of the palate, and came to the following conclusions:-

1. Glycogen is found where there is parakeratosis, and it is absent where there is hyperkeratosis.
2. Acanthosis and inflammation are seen in areas where there is glycogen deposition. No relationship is inferred from this study.

3. Glycogen is seen in the prickle cell layer, in "fissures" around epithelial pearls, and rarely, in the basal cells.
4. In some instances, vacuolated epithelial cells contain heavy deposits of glycogen.

Santis et al (1964) investigated the histochemistry of experimentally induced leukoplakia and carcinoma of the hamster buccal pouch. Repeated application of D.M.B.A. (9,10 dimethyl 1,2 benzanthrane) resulted in a large number of epidermoid carcinomas, usually invasive, but well differentiated. Of particular interest was the development of a lesion characterized by hyperkeratosis and dyskeratosis, which was analogous to the leukoplakial lesion of human oral mucosa. Carcinoma was often seen to arise within or adjacent to these leukoplakial areas, and the interpretation of the latter as areas of premalignancy or early malignancy must be justified.

Furthermore, the histochemical enzyme studies appeared to suggest that the leukoplakic areas represented a transitional type of lesion between normal mucosal epithelium and carcinoma. In fact, the reaction of these areas of premalignancy was more similar to the reaction of epidermoid carcinoma than to that of normal epithelium. Thus, these zones may be considered early malignant neoplastic lesions.

The histochemical reactions corroborated numerous previous studies demonstrating an altered metabolism in malignant neoplastic tissue. The metabolic significance of these enzymes (acid phosphatase, alkaline phosphatase, non-specific esterase and B-D-galactosidase) has not been completely established, but it has been suggested that acid

phosphatase is related to the process of keratinization, and Santis et al's observations appeared to corroborate these findings. In all cases, enzyme activity appears to be localized primarily to cellular cytoplasm and intercellular substance. Enzyme activity in cell nuclei, if present, could not be demonstrated by these histochemical techniques. Zelickson also states that enzymes are stored in the mitochondria and function in the cytoplasm of cells.

Malignant lesions were characterized by increased acid phosphatase, alkaline phosphatase and beta-D-galactosidase activity, and decreased esterase activity. A transitional or premalignant zone, with many features similar to human oral leukoplakia was noted. These areas presented enzyme "activity patterns" similar to those exhibited by carcinoma, but were less reactive.

Niebel and Chomet (1964) have made a preliminary report describing an in vivo staining test, using toluidine blue for the clinical delineation of intraoral dysplasia and in situ carcinoma. Richart recently described this method for the delineation of dysplasia and carcinoma in situ of the cervix of the uterus.

All suspicious areas were stained with toluidine blue, as part of the clinical examination. Toluidine blue is a nuclear stain which will demonstrate the crowded cells of the dysplasia and the in situ carcinoma. Richart reported that "the intensity of the stain is correlated with the nuclear density, and the severity of the neoplastic process can be gauged roughly from the shade of blue, which ranges from a pale blue in minimal dysplasia, to a very intense royal blue in carcinoma in situ, or early invasive carcinoma".

In the experience of Niebel and Chomet, the early malignant lesions were sharply delineated from the non-neoplastic epithelium, and stained more intensely. The small, nonmalignant, traumatic ulcers frequently confuse the picture. The stain is retained at the site of inflammatory infiltrate that is associated with eroded mucosa. These areas, however, soon lose their stain in the decolourizing process, whereas areas of dysplasia and carcinoma in situ retain the stain much longer. The latter are almost impossible to blanch completely, according to Richart.

Shiller's iodine test was previously used by Niebel and Chomet in an attempt to identify clinically the intraoral tissue suspected of malignant change. This test is based on the absence of glycogen in the cancerous tissue as opposed to normal squamous epithelium which is rich in glycogen. The normal tissue combines with iodine to form a mahogany-brown stain, while the active proliferating epithelium remains poorly stained or unstained. Unfortunately, certain benign neoplasms may fail to take the stain, and certain keratinizing cancers may contain glycogen and stain faintly. The test was not sufficiently accurate and was discarded. Burket (1961) mentions a similar test with Lugol's iodine.

Niebel and Chomet conclude by saying that this simple in vivo staining test has been accurate in delineating intra-epithelial neoplasms of the oral mucous membrane. It has been of assistance to the surgeon by enabling him to determine the site and extent of the lesion. This procedure may provide the clinician with another valuable tool for the diagnosis and treatment of intraoral cancer.

Aetiology.

Various causative factors in leukoplakia are cited by numerous authors:-

Hollander et al (1933); Local factors - tobacco (very important), alcohol, dental irritation, hot spicy foods, cheek-biting, galvanism, Systemic - syphilis, neurasthenia, gouty diathesis, diseases of stomach.

Kanner (1938); discounts the effects of galvanism.

Reed and Willman (1940); discount the effects of galvanism, saying that a current large enough to be harmful would quickly dissolve fillings.

Ziskin (1941); Parenteral injection of the male sex hormone causes hyperplasia of all layers of the epithelium and corium.

Hobaek (1946); Most important is dental irritation - poor hygiene, jagged, carious teeth (in 12 of 246 patients), badly fitting prostheses (in 29 of 246 patients). Tobacco was not considered as important as in earlier studies, the importance of alcohol was unconfirmed, galvanic action was unimportant. Underlying the suffering must be a predisposition, possibly activated by leutic infection, (but Hobaek states this appears to be less important than formerly - in 8.1% in his study, and then mostly connected with leukoplakia of the tongue).

Curtis and Slaughter (1947); Local factors - dental irritation, artificial dentures, faulty occlusion, poor oral hygiene, tobacco, any physical or chemical trauma. Systemic - syphilis, avitaminosis A, inherited susceptibility.

Martin (1948); Leukoplakia of the oral mucous membrane occurs as a result of a response of the tissue to chronic irritation, and is often found to precede or be associated with cancer. These two conditions have a common aetiology so far as chronic irritation is concerned. The aetiological significance of chronic irritation from sharp or broken teeth and ill-fitting dentures has undoubtedly been greatly overemphasized.

Sharp (1948); The aetiology is the same as for cancer. Chronic inflammation from exposure, chemical and thermal irritants, trauma, dental factors, constitutional disease. Individual predisposition or susceptibility.

English (1949); Chronic irritation from tobacco, rough edges. Predisposing factors, avitaminosis B, and syphilis.

McCarthy (1949); Chronic irritation from faulty occlusion, carious teeth, galvanism (not proven), hot, spicy foods, tobacco chewing, chronic periodontal infection, betel nut quid, vulcanite denture improperly cured, tobacco (the most important, the method of smoking being significant), syphilis (atrophic glossitis the main factor).

Predisposing factors; avitaminosis A (autopsy studies showed that one-third of all individuals beyond middle life show leukoplakia of the oesophagus), hormonal imbalance.

Ward and Hendrick (1950); Secondary to some form of chronic trauma.

Effect of syphilis small except in the case of leukoplakia

Schreiner and Diamond (1952); There is good evidence that serious pathologic conditions are caused by metallic dental fillings. The size of the current is not important. More important is the sensitivity of the patient to metallic ions supplied by fillings.

Schaffer (1952); Local - the effect of dental irritation has been overstressed, chronic irritation of tobacco, galvanic current or rough teeth can hardly be considered aetiological. Systemic - inherent tendency to hyperkeratosis, possibly acquired by general somatic disturbances such as endocrine dysfunction, avitaminoses and other metabolic conditions.

Kreshover (1952); Experimental evidence was presented to substantiate the contention of many that predisposing factors are of importance in tissue response to tobacco and that the irritant may be merely an extrinsic exciting factor. His findings suggested that vitamin B deficiency increased susceptibility to the smoke irritant, whereas gonadectomy established an appreciable degree of resistance. The action of the tongue and saliva quickly removes deposited tars and probably provides protection.

Karshan et al (1953); No consistent correlation was found between lesions and any definite systemic factors. Of 25 patients, there was a marked preponderance of middle-aged women. Emotional disturbances were associated with exacerbations, previous hysterectomy and menopause were frequently reported. Cancerophobia was marked.

Laband and Bumsted (1955); 12 premalignant changes of the lower lip.

The causative factors were a predisposing fair complexion and extreme exposure to sunlight.

Kreshover (1955); Experiments in mice showed that riboflavin,, pyridoxine, and pantothenic acid are the B complex components primarily responsible for alterations in tissue response. The latter was a proliferative change characterised by hyperkeratosis; hyperplasia, acanthosis and chronic inflammation of the corium. Cellular alterations in size, shape and staining qualities, as well as loss of basal cell polarity and increased mitotic activity, indicate the abnormal activity of the tissue change.

Boyle (1955); Local causes - smoking (products of combustion), juice of chewing tobacco, alcohol, hot or spicy foods. Systemic - tertiary syphilis (particularly for the tongue), deficiency of vitamins A and B.

Cheraskin and Langley (1956); Local - chronic irritation due to smoking, very hot or cold foods, condiments, rough fillings, caries, ill-fitting dentures. Predisposing - syphilis, vitamin deficiency states (especially hypovitaminosis A), and endocrine dysfunction.

Hertz (1956); Local factors - (1) tobacco and undiluted alcohol play a very great role which is, practically speaking, an established fact. He quotes Hayes Martin's figures that 98% of patients with oral carcinoma are heavy smokers. (2) diseases of the teeth, oral cavity, and galvanism are important.

- Systemic - (1) syphilis; Hertz quotes the following figures:- (a) Hayes Martin - 6% male population at 56 years (cancer age average) have positive Wassermann reaction, (b) Nielsen - 10% patients with oral cancer and 18% with tongue cancer have a positive Wassermann.
- (2) Ariboflavinosis (vitamin B deficiency) may exercise an influence by reducing the ability to absorb iron from the intestine.
- (3) Iron deficiency is fairly important.
- (4) Age is important.

Sharp et al (1956); Predisposing factors - prolonged inadequate diet, particularly vitamin B complex deficiency and low protein intake, individual constitutional variations. Local irritating factors - dental factors (jagged teeth, ill-fitting dentures, oral sepsis), climate and exposure, (in leukoplakia of the vermilion border of lip), chemical irritants, thermal irritants, mechanical irritants.

Weisberger (1957); Tobacco (order of importance - pipe, cigar, chewing, cigarette). Ageing is important. Postmenopausal women, non-smokers, with leukoplakia showed regression in many cases when treated with oestrogens; macrocytic anaemia often present. Syphilis is a factor - in 14 patients with oral leukoplakia and syphilis, the incidence of carcinoma developing at sites of leukoplakia was 100%.

Toto (1957); Chronic irritation predisposes to leukoplakia and carcinoma.

Wynder et al (1957); The same factors that are important in the aetiology of oral cancer are operable in the aetiology of leukoplakia. Smoking - an important factor. The fact that male oral cancer has not increased with the increase in cigarette smoking is consistent with the fact that the relative risk of mouth cancer is greater for pipe and cigar smoking, which has decreased. There has been a small increase in incidence in women, but most have not smoked for long enough for the effects to appear. Alcohol - heavy consumption is a factor. The relative risk of cancer rises very sharply among heavy drinkers. Syphilis - a significant relationship in the anterior two-third of the tongue and in the lip. They were unable to determine the influence, if any, of arsenical therapy. Plummer-Vinson's Syndrome - may be caused partly by alcoholism. Responsible in part for the relatively high mouth cancer rate in Swedish women. In addition to a chronic iron-deficiency state, it probably also involves other nutritional deficiencies, notably vitamins B and C. Dental Factors - not major factors. Edentia was more common in the study group, and these writers question whether the factor causing edentia was also operative in causing the cancer. Exposure to sunlight - lip cancer is more common in sunny countries. Betel-nut smoking and betel-nut chewing are significant in India.

Renstrup (1958); In the series of 100 cases, 42 were connected with local irritation; 23 with tobacco; 19 with sharp or carious teeth, faulty dental restorations, dental calculus, clasps. Three patients had positive Wassermanns.

Fasske et al (1959); Exogenic factors - mechanical trauma, ill-fitting dentures and smoking. Endogenic factors such as metabolic disturbances (e.g., diabetes mellitus). In 50% of cases, neither type of factor could be established.

This idiopathic type occurs mainly in senescent patients.

J.A.M.A. 169:1695, April 4, 1959; There is no definitive evidence to support the view that metallic fillings of varying electrical potentials predispose to oral leukoplakia.

Sutherland (1959); Aetiology obscure - irritants such as smoking, sepsis, spirits, spices, broken teeth, faulty dentures; play a part. Syphilis predisposes.

Bernier (1959); For "pachyderma oris" - local factors are bad dentures, clasps, fillings, drugs (astringents) foodstuffs. Predisposing - a possible conditioning factor.

For "leukoplakia" - the aetiology is unknown. It is possible that the origin of "leukoplakia" and carcinoma may be the same. Chronic trauma in any form is important. Irritation from dental sources plays a part. In the act of smoking, the following factors are important:-
trauma, heat, smoke and the combustion products of tobacco. Pipe and cigar smoking seems to be more harmful than

cigarette smoking because of concentrated heat. The role of galvanism, alcohol, and condiments requires clarification.

Bernier describes as an entity, "senile keratosis", but to this reviewer such a distinction appears to be unnecessary, as the features and aetiology described seem to indicate that it is merely a form of leukoplakia.

Silverman and Ware (1960); Local factors - smoking and exposure to coal-tar products have long been under suspicion.

Clinical evidence indicates a more basic second or predisposing factor.

Chapman and Reddish (1960); There are multiple well-fortified clinical observations to indict pipe-smoking as the predominant offender.

Thoma and Goldman (1960); The usual chronic irritation factors are mentioned. As possible predisposing factors, hypercholesteremia and allergy to food may play a role.

Waldron and Shafer (1960); There is considerable evidence of the importance of tobacco, the regression of some lesions on cessation of smoking being evidence of a cause and effect relationship. The role of multiple co-existing predisposing factors, such as liver damage, tobacco, alcohol, is mentioned. The effect of syphilis is a minor one. Vitamin A and B deficiencies seem to be significant, but hormonal influences seem small. The effect of galvanism is discounted as a significant aetiological factor.

Orban and Wentz (1960); For hyperkeratosis simplex - sometimes idiopathic. Local factors; cheek biting and denture irritation. Predisposing factors; syphilis, iron-deficiency anaemia, vitamin A deficiency.

For hyperkeratosis complex - long continued irritation and possible modification by unfavourable systemic, hormonal, nutritional and genetic factors.

Shafer and Waldron (1961); The data on the aetiology of lesions in this study was not sufficient to enable any conclusions to be drawn.

Bhaskar (1961); For "pachyderma oris" - there may be associated an apparent cause, such as lip biting, or the cause may be obscure.

Wrubel and Scopp (1961); No definite change in the pattern of oral exfoliative cytology could be observed following the cessation of smoking in a group of volunteers. The findings did not preclude the possibility that smoking may affect oral keratinization patterns; under the limitations of this experiment, the difference could not be ascertained.

Archer (1961); Local irritants - smoke or snuff, strong condiments, alcohol, dental trauma, hot spicy foods, galvanism. Predisposing causes - allergy, avitaminosis A, and hypercholesteremia.

Burket (1961); Local irritants - sharp teeth, bad dentures, caustics, tobacco, poor oral hygiene, galvanism. Predisposing - constitutional characteristics, as people with blond skin and blue eyes are said to be more likely to develop the disease. Nutritional - hypovitaminosis A and B; Endocrine, gonadal disturbances. Systemic disease; syphilis important in leukoplakia of the tongue. In 50% of patients, no cause can be discovered.

Arnott, A.J. (1962); A quantitative and qualitative dietetic analysis should be made for each patient with white lesions. Vitamin deficiency, plus local irritation may well be the causative factors.

Stones (1962); Local irritation from heavy smoking, strong alcohol, cheek biting.

Predisposing causes - dietary deficiency; hypovitaminosis A and B. Heredity - some members of the same family have white lesions. (Note; Stones quotes Cannon (1935) in this regard. Cannon was one of the first reporters of white folded gingivostomatitis). Endocrine changes may have some influence. When syphilis is superimposed on a leukoplakia it is more likely to undergo malignant changes.

Rushton and Gooke (1963); Friction and smoking are external irritants that frequently precipitate this anomaly, but some individuals have a lower threshold to keratinization than others.

Hellinger et al (1963); Stimuli of varying duration lead to "leukokeratosis" - hyperkeratosis, or hyperkeratosis and acanthosis. When lesion is atypically located and/or macroscopically irregular in appearance and associated with an undetermined stimulus, there is a lower percentage of positive correlation (of clinical features and histologic features) as well as a statistically high incidence of "dysplasia". The term "leukoplakia" should be reserved for those cases in which the lesion is clinically abnormal and/or occurs at an unusual site. Smoking is a conditioning factor rather than a direct cause.

Shafer, Hine and Levy (1963); Local influences - tobacco; there is much evidence for its importance, the combustion products, heat, and juices from chewing tobacco, all playing a part, pipe smoking is directly involved in the aetiology of "stomatitis nicotina", while studies of Roffo showed that tobacco smoke blown on the gingiva of rabbits soon produced white spots. Regression of some lesions after cessation of smoking is further evidence of a cause and effect relationship. Any chronic irritating factor in the oral cavity, such as cheek-biting, ill-fitting dentures, or sharp teeth should be suspected. Hot spicy foods may be of some importance. Galvanism's importance is discounted. Predisposing factors; A number of workers (Sharp, 1948, Wynder et al, 1957) have suggested that the same factors that are important in the aetiology of oral cancer are operable in the aetiology of leukoplakia. The role of

liver damage, tobacco and alcohol, as emphasized by Trieger et al (1958-9) are mentioned. The importance of syphilis is discounted except in the case of leukoplakia of the tongue. Current literature gives little clinical support to the role of endocrine dysfunction, and the deficiency of vitamins A or B, and there has been a general lack of recent investigations of these factors, making their significance in the aetiology of leukoplakia difficult to evaluate.

Quigley et al (1964); In a preliminary study of the reverse smoking habit and its effects on oral health, 21 subjects, (19 women, 2 men) were examined thoroughly. Generally, the oral cavity had heavy tar deposits on the buccal and lingual surfaces of the teeth, tough, hard, leathery palate, reduced flow of saliva, and leukoplakia on the palate and lips. Biopsy and cytology did not reveal dysplasia.

Sharp, Bullock and Helsper (1963); attempted to determine the conditions that contribute to the development of multiple carcinomas. Their findings supported the theory that the mucous membranes of oral cancer patients were atypical, even in the "normal" areas adjacent to the actual carcinoma. It was their impression that atrophy precedes leukoplakia and that no one oral surface seems to have a special tendency toward development of subsequent primary cancers. It appears that atrophy and hyperplasia are the basic pre-cancerous changes.

McCarthy and Shklar (1964); Exciting (local) causes - local irritation due to sharp, malposed teeth, ill-fitting dentures and poor restorations. Occlusal disharmony is of significance in causing irritation, as are occlusal traumatic habits, such as tongue or cheek biting, thrusting the tongue against the teeth or lips.

Smoking is to be regarded as an irritant, presumably because of the drying effect on the mucosa, the products of combustion and the heat. Local irritation, including smoking, is to be regarded as the primary exciting cause of leukoplakia. Continuous irritants such as hot drinks and spicy foods may be a factor, also irritating mouth-washes. Syphilitic glossitis may be a factor, but the number of syphilitic lesions of the oral mucosa is negligible, and the importance of syphilis as a causative factor in leukoplakia is to be minimized.

Predisposing (systemic) causes; The exciting factors presumably must act in a susceptible host, and heredity doubtless plays an important role in determining the individual's susceptibility or resistance to the development of leukoplakia. Systemic predisposing factors or conditioning factors may be hormonal alterations and nutritional deficiencies. Oestrogen deficiency may determine the susceptibility of females at the menopause. Vitamin A deficiency can produce a hyperkeratosis in

experimental animals, but this reaction has not been adequately demonstrated in human beings, and therapy based on this assumption is not justified at present.

Vitamin A Deficiency.

Many of the above authors ascribe an important part of the aetiology of leukoplakia to the predisposing effect of vitamin A deficiency. It has assumed such importance that separate consideration will be given to it.

Wolbach (1937) found that the seat of the physiologic disturbance in vitamin A deficiency is in the epithelial cell, and that even though the chemical role of the cell is suppressed, the proliferative powers are not lost. In vitamin A deficiency, the sequences are atrophy of the epithelium concerned, and substitution for it by a stratified keratinizing epithelium. The basal cells normally contained in maintaining the integrity of the epithelium respond by active mitotic division. Scattered areas of proliferation appear beneath the original epithelium. The new cells by their continued growth undermine and replace the original epithelium, and, regardless of the previous structure and function of the region, develop into a stratified keratinizing epithelium.

Schour and Massler (1945) reported that experimental work showed that vitamin A deficiency resulted in the failure of epithelial cells to differentiate. The basal cell layer loses its type specificity, and tends to produce a stratified keratinizing epithelium regardless of the type previously formed. The failure

to differentiate allows the basal cell layer to continue its proliferation unchecked. A keratinizing metaplasia results in numerous epithelial structures throughout the body. In man vitamin A deficiency may result in hyperkeratotic changes in the oral mucosa.

This reviewer considers use of the term "failure to differentiate" inapplicable here. Keratin can not be produced unless there is differentiation, in fact if there is no differentiation, nothing can be produced. Neither does the basal layer continue its proliferation unchecked, on the contrary, mitosis has been shown to be diminished.

Rowe and Gorlin (1959) found that vitamin A deficiency promoted epithelial tumour production in the carcinogen-treated pouch of the hamster.

Orban and Wentz (1960) state that the concept that some forms of hyperkeratosis may occur in patients conditioned by long-standing vitamin A deficiency has gained increasing support, especially when the hyperkeratotic oral lesions show a rapid return to normal with the administration of large therapeutic doses of this vitamin. Intestinal disturbances are frequently the cause of insufficient absorption of vitamin A.

Thoma and Goldman (1960) quote the work of Wolbach and Bessey who showed that a deficiency causes metaplasia in epithelium having secretory function, particularly the salivary glands.

Mercer (1961) seems to have a slightly different concept of the affect of vitamin A deficiency. He quotes Fell and Mellanby et al as showing that vitamin A disposes the epidermis towards mucin formation and that the change is reversible. He also quotes the work of Lasnitski who found that embryonic epidermis in normal medium formed a typical squamous keratinizing epithelium. In a medium containing vitamin A, several layers of large cuboidal cells appeared which contained mucin-like materials. Older skin is less responsive, but vitamin A suppressed keratinization. Mercer states later that cells in the process of keratinization can still be deflected in their course by the vitamin, but that mucin-forming cells once formed cannot revert when returned to a normal medium, but are shed. He emphasizes that the adaptive response of the epidermis to hard work may be produced by dissipation of "inhibitor" resulting from friction and pressure, rather than by stimulation.

Stones (1962). In adults, there is a possible association between vitamin A deficiency and hyperkeratosis of the oral epithelium and leukoplakia. He also quotes the effect in laboratory animals.

Shafer, Hine and Levy (1963). In vitamin A deficiency the epithelial cells fail to differentiate. This means that the cells in the basal layer lose their specificity and tend to form a stratified squamous epithelium with keratin production, independent of the type of cell previously formed by the basal cells. Thus one of the basic changes is a keratinizing metaplasia of epithelial cells.

III

Silverman et al (1963) A series of "Studies in Oral Leukoplakias," are being carried out by a number of workers, the leading members being Silverman, Renstrup and Pindborg. Particular attention is being paid to the role of vitamin A, based on their observations of previous topical vitamin A therapy, which make it evident that in some patients large doses of vitamin A are able to alter keratinization and at least temporarily induce partial or complete disappearance of leukoplakia.

16 Patients were given daily fractionated doses of vitamin A troches, totalling 300,000-900,000 units per day for 1-15 weeks. Four had complete remissions, three partial disappearances. After withdrawal of vitamin A, all recurred to some extent. Clinical remissions were reflected by microscopic changes of lessened hyperkeratoses and/or mucous metaplasia. Cytologic scrapings showed increased basophilia and nucleation. Serum levels of vitamin A were markedly increased, but there were no apparent correlations with clinical remissions. Five patients demonstrated skin lesions and pruritis, which disappeared within two weeks after withdrawing the vitamin.

The evidence obtained supported the theory of local tissue accumulation by direct absorption. Human as well as animal studies show that vitamin A increases the M.I. It was assumed that this increased turnover rates, and so precluded keratin cornification because of lack of time.

It has been assumed that a yet unidentified intermediary

metabolic degradation product of vitamin A may interfere with sulphhydryl metabolism, thus impairing the formation of keratin. There is an indication that the differential effects of vitamin A are reflections of distinctive patterns of enzyme distribution.

A further study was carried out by this group (Silverman et al VII, 1963) of 19 patients treated with vitamin A acetate given as 75,000 unit troches, resulted in complete remission in five, partial remission in ten, no change in four. All demonstrated recurrence two weeks after withdrawal of vitamin A. The epithelium was transformed microscopically to lesser degrees of cornification or became unkeratinized. Cytological scrapings showed tendency towards a decrease of denucleation and cytoplasmic acidophilia. 11 of the 19 patients showed side effects - dry skin, pruritis, a skin rash. These disappeared in two weeks after discontinuation of therapy.

Smudski and Myers (1963). It can be inferred that vitamin A, in some manner, participates in the regulation of the metabolism of sulphur. Keratin has a high proportion of the sulphur-containing amino acid cystine. Experiments with vitamin A deficient animals (rats) showed a decrease in total sulphur output, of which a greater proportion was as sulphate.

McCarthy and Shklar (1964). Vitamin A deficiency has been shown to produce hyperkeratosis of the oral epithelium in experimental animals, but its role in oral lesions in human beings has not been clarified. Because of the animal findings, it has been postulated

that vitamin A deficiency may be related to leukoplakic lesions of the oral mucosa in human beings, and vitamin A has been suggested as a therapeutic agent in cases of oral leukoplakia. Their observations have not tended to corroborate this work.

Jolly (1964). Experimental evidence from the study of vitamin A deficient animals disclosed the following findings relevant to this subject:-

1. The salivary gland epithelium of the albino rat is very susceptible to vitamin A deficiency, producing severe xerostomia.
2. No macroscopic changes are produced in the oral mucous membrane by vitamin A deficiency except perhaps that it becomes slightly paler.
3. The subepithelial tissue assumed the appearance of connective tissue hyalinization.
4. There was disruption of the normal orderly arrangement of the basal epithelial cells and a loss of the normally well-defined margin between them and the lamina propria.
5. Cells morphologically similar to melanocytes were observed in increased numbers in the oral epithelium of the depleted animals.
6. Where there is "complete orthokeratinization" in the stratum corneum of the hard palate, the changes produced, including

reduction in thickness and loss of cellular and nuclear detail, are almost entirely atrophic in nature.

7. Where there is incomplete "orthokeratinization" in the stratum corneum of the cheek, soft palate, and inter-papillary areas of the tongue, the epithelium undergoes metaplasia and comes to resemble the epithelium of the hard palate. The reduction of thickness in the epithelium is due in the case of; the soft palate - to metaplasia; the cheek mucosa - to metaplasia largely, to a lesser extent, to atrophy, the cornified layer being reduced by metaplasia mainly, and wear and tear from mastication; the tongue - to metaplasia.
8. The basement membrane is disrupted in the deficient animals.
9. A substantial reduction in thickness of the epithelium occurred in each of the locations studied, the greater part occurring in the cellular part of the epithelium.
10. There was a vast reduction in the rate of mitosis in the oral epithelium.

These changes shown in vitamin A deficient rats are a little difficult to compare with those found in the human mucosa when leukoplacic changes occur. The basic divergence is, of course, the absence of whiteness in the rats, and this in turn is related to the other major difference, the reduction in thickness of the epithelium. The stratum corneum must be thickened for a white lesion to occur.

The measurement of overall thickness of the epithelium in white lesions does not appear to have been specifically studied elsewhere, but a perusal of the histopathology of leukoplakia described by various authors reveals that most state or imply that the epithelium is thickened. From the figures of Shafer and Waldron (1961) it can be deduced with some certainty that at least 65% of their series showed thickening of the epithelium, while in the series of Cahn et al (1961 & 1962), a reasonable inference is that all 88 leukoplakic lesions showed thickening of the epithelium.

The fact that vitamin deficiencies in humans are rarely total or even single, could account for the differences mentioned, and in this regard, it would be most interesting to see the results of a study carried out to determine the effects in rats of a partial vitamin A deficiency sustained over a longer period than the maximum of about 26 weeks of Jolly's study, and carried out at a later stage of the animal's life, to duplicate the age incidence of leukoplakia in humans.

For the present, it appears that the role of vitamin A in the aetiology of leukoplakia awaits further clarification.

Summary.

The opinions of 36 authors on the aetiology of leukoplakia have been reported. An analysis of these has been made with the following results:-

Local causes;

16	Authors	found	smoking	significant.
15	"	"	sharp teeth	"
11	"	"	ill-fitting dentures	"
11	"	"	poor restorations	"
8	"	"	irritant chemicals	"
6	"	"	irritant foods	"
5	"	"	galvanism	"
5	"	"	thermal factors	"
5	"	"	occlusal habits	"
3	"	"	occlusal disharmony	"

Predisposing causes;

18	Authors	found	nutritional factors	significant.
16	"	"	syphilis	" (mainly for the tongue)
8	"	"	hormonal factors	"
5	"	"	heredity	"

Diagnosis.

The diagnosis of leukoplakia is made on the basis of clinical observation. The grade or type of leukoplakia and the possibility of a premalignant lesion can be determined conclusively only on the basis of microscopic studies. The clinical picture may suggest a premalignant or dysplastic lesion, but only biopsy can confirm this. Often a small innocuous appearing area of leukoplakia may represent a premalignant or even a malignant lesion. Biopsy is imperative in cases of leukoplakia. In the diffuse type involving large areas of the mouth, two or multiple representative biopsy specimens may be desirable. In general, McCarthy and Shklar (1964) feel that leukoplakial lesions do not alter microscopically except in rare cases. A simple hyperkeratotic lesion does not change into a dyskeratotic lesion. They suggest that this type of change would require a cellular mutation rather than a simple hyperkeratotic response to some irritant. Therefore, therapy will be predicated upon the microscopic appearance of the lesion and the presence or absence of dyskeratotic changes.

Of the numerous authors consulted, not one actually disputes the need for biopsy for diagnosis and treatment planning, and there seems to be no point in listing all the names of these authors. However, varying emphasis is placed on the need for biopsy according to the view of the individual author as to whether he can deduce the microscopic picture, and therefore the future behaviour of the lesion, from its clinical appearance. The majority of authors take the view expressed by Shira (1964) that biopsy specimens should be obtained

from every persistent white lesion of the oral mucosa that cannot be otherwise identified by its own particular characteristics, (lichen planus, psoriasis, etc.).

A divergence of opinion is presented by Chapman and Reddish (1960) who aver that correlation of the severity of the lesion estimated clinically with that graded histologically is excellent.

Chomet et al (1962) appear to place considerable reliance on their ability to distinguish innocuous and premalignant lesions as they describe three categories; (1) the simple "leukoplakias" (their definition of leukoplakia being hyperplasia, hyper- or parakeratosis, and inflammation); (2) the suspicious lesions, and (3) the probable early carcinomas. Towards the end of their article, they mention that "leukoplakias" were infrequently biopsied, saying that only if there was clinical doubt was biopsy performed. In this reviewer's opinion, this statement invalidates any figures they present, as it would be impossible to state with certainty the nature of the lesion without histologic examination.

A recent article by Hellinger et al (1963) attempts to correlate the clinical features with histopathologic features, and also aetiological factors. Much of the article is well presented and logical, particularly when relating the type and duration of stimulus to the tissue response. For example, it is suggested that if the inciting agent is of short duration, hyperkeratosis ensues, if of longer duration, acanthosis is present also. However, the

attempt at correlation is unconvincing, as many of the cases appear to have been white lesions of a transitory nature which usually would not have been included in a series, while the difficulty of determining a specific and single stimulus is glossed over.

Furthermore, the authors describe a group as being of "undetermined aetiology" which was hallmarked by atypically located lesions showing a high percentage of histologic correlation as either dysplasia or carcinoma. The net effect of the article for this reviewer is to reinforce the opinion that "biopsy specimens should be obtained from every persistent white lesion of the oral mucosa that cannot be otherwise identified by its own particular characteristics".

Pindborg et al (1963 V) take the point of view that leukoplakias characterised by the presence of white patches, either in a nodular form or as more diffuse, white lesions interspersed with erythematous areas, are often associated with either epithelial atypia or carcinoma. Therefore the "speckled" type should be excised or followed with great care.

At the beginning of this section the opinion of McCarthy and Shklar was quoted that a simple keratotic lesion does not change into a dyskeratotic lesion. Gorlin (1957) also states that there is no good evidence that simple hyperkeratosis ever changes to leukoplakia or gives rise to any true neoplasm. Shira and Bhaskar (1964) present a case report which showed apparent progression from a benign hyperkeratotic lesion to advanced squamous cell carcinoma in eight years.

Again, Smith (1960) presents a case report describing the course of a lesion in the left buccal mucosa of a snuff taker, five biopsies being taken, showing in:-

- 1951 - benign hyperplasia and hyperkeratosis,
- 1952 - benign hyperkeratosis with parakeratosis,
- 1953 - verrucous hyperplasia with unusual cellular activity,
- 1955 - dyskeratosis with a malignant pattern,
- 1957 - epidermoid carcinoma and invasion.

West (1962) presented a case of leukoplakia diagnosed by biopsy, and followed from 1948 to 1957. The patient died of primary epidermoid carcinoma of the gingiva related to the leukoplakia. The oral lesion had been present for 14 years.

A few cases are not particularly significant, but this reviewer feels that the "cellular mutation" required by McCarthy and Shklar may occur when there is chronic irritation and the "X" predisposing factor is operating. Despite the protective nature of the hyperkeratotic covering, it seems a completely unwarranted assumption that the cellular mutation could not occur in such a lesion.

Differential Diagnosis.

McCarthy (1949); Syphilis - the chronic mucous patch sometimes has a silver sheen resembling leukoplakia, but other signs of syphilis are present. Lichen planus - if there are no extraoral lesions, differentiation is difficult. Clinical features may be distinctive, lichen planus usually being symmetrical. Microscopic

picture may be confused, but lichen planus usually has less hyperkeratosis, the cellular reaction more intense and sharply demarcated, tending to obliterate the rete cones. Lupus erythematosus shows superficial ulceration surrounded by a zone of whitish tissue, resembling leukoplakia, irregularly distributed. Exudative processes - distinguished by the ready removal of the exudate.

Ward and Hendrick (1950); From syphilis, by serological tests, from carcinoma, by biopsy, from lichen planus and psoriasis.

Salman and Langel (1954); From lichen planus; Leukoplakic lesions can form over an area of lichen planus, making diagnosis difficult. Even biopsy may not be conclusive.

Sharp et al (1956); A leukoplakic process can form over an area of lichen planus, in which case the diagnosis becomes difficult. Because of the resemblance, microscopically, between leukoplakia and lichen planus, the differentiation may be difficult, even with a biopsy.

Orban and Wentz (1960); For hyperkeratosis simplex,
1. Lichen planus, 2. Moniliasis, 3. Epithelial hyperplasia, 4. Lupus erythematosus, 5. Hyperkeratosis complex, 6. Carcinoma. The diagnosis is made by biopsy and correlated clinical appearance and history.
For hyperkeratosis complex; 1. Lichen planus, 2. Moniliasis, 3. Epithelial hyperplasia, 4. Lupus erythematosus, 5. Herpes simplex, 6. Epidermoid carcinoma.

Diener (1961); This case report of "leukoplakia buccalis" occurring in a woman of 21 years, having been present for 17 years (!!) is mentioned to illustrate a lack of differential diagnosis. The patient's history must have been completely unreliable.

Archer (1961); From lichen planus, pemphigus, erythema multiforme, herpes, syphilis, chemical burns, moniliasis. All except lichen planus are easily wiped off.

Burket (1961); From traumatic irritation of the cheek mucosa, lichen planus, and more rarely, oral miniliasis. Extensive white lesions occurring in children, especially when present in several members of a family, should cause one to consider white folded gingivostomatitis.

Lichen planus has a more diffuse outline, no change in pliability, and the general distribution will help in differentiation. Lugol's iodine test—normal tissues take a deep mahogany stain, leukoplakia does not stain, traumatic cheek lesions take a deeper stain, lichen planus does not take much colour change. Biopsy is necessary.

Castigliano (in Burket, 1961); Recommends biopsy whenever hyperplasia or piling-up or thickening appears in the leukoplakic area, but sometimes malignant change occurs without visible alteration. Multiple biopsy may be needed.

Shafer, Hine and Levy (1963); Lichen planus is the most important lesion to be differentiated. Usually the clinical features will distinguish it, but biopsy is necessary in some cases.

Other white lesions to be differentiated include chemical burns, syphilitic mucous patches, mycotic infection (chiefly moniliasis), psoriasis, lupus erythematosus and white sponge naevus. Burket's test with Lugol's iodine is mentioned. Biopsy is necessary for differentiation in many cases.

McCarthy and Shklar (1964); Lichen planus; plaque-like lesions of lichen planus may resemble leukoplakia very closely. If the papular nature of the lichen planus lesions cannot be discerned, then biopsy may in some cases reveal the classic pattern of lichen planus. Lichen planus may present skin lesions, while leukoplakia is confined to the oral cavity.

Discoid Lupus Erythematosus; Chronic discoid lupus erythematosus may present oral lesions somewhat similar in appearance to the initial localized lesions of leukoplakia. Skin lesions are usually present in lupus, and a biopsy will reveal a characteristic pattern of perivascular inflammatory infiltration and collagen degeneration as well as hyperkeratosis and hydropic degeneration of the stratum germinativum.

Oedema (leukoedema); Occasionally oedema of the buccal mucosa along the occlusal line of the teeth may present a white-grey appearance resembling the initial lesions of leukoplakia. Biopsy will reveal an absence of hyperkeratosis and considerable oedema of epithelial cells, particularly in the stratum spinosum.

Carcinoma; An epidermoid carcinoma may resemble a lesion of leukoplakia, usually of the severe localized variety with induration. Biopsy will reveal the characteristic features of a malignant lesion.

Traumatic lesions; Either chemical or thermal traumatic lesions may appear as a white raised area because of necrosis of the surface epithelium. This white surface slough can be easily wiped off, leaving a raw ulcerated area.

Moniliasis; The lesions of acute moniliasis or thrush may present as white plaques and resemble leukoplakia superficially. These areas represent extensive overgrowth of *monilia albicans*, and the mycotic organisms invade and destroy the epithelium. Smears will reveal the organisms either in spore or mycelial patterns. The monilial plaque areas are easily scraped off the mucosa, leaving an ulcerated zone.

Comments.

It is evident that in most cases, differential diagnosis, though difficult, can be made by careful consideration of the clinical features, together with biopsy. The most difficult differentiation to be made is that from lichen planus, as McCarthy (1949), Salman and Langel (1954) and Cahn and Slaughter (1962) point out that leukoplakia may be superimposed on lichen planus, even biopsy not necessarily being conclusive. Further consideration of this factor will be given in the section on lichen planus.

Therapy and Management.

Hollander et al (1933); Antisyphilitic if necessary.

The use of tobacco and alcohol should be eliminated, and any sources of irritation removed. If the lesions remain at the end of 14 days, they should be removed by electrodesiccation.

Abels et al (1942); Daily doses of brewer's yeast resulted in remission of leukoplakia in from 2 to 10 months.

Gibbel, Cross and Ariel (1949); Reported complete disappearance of leukoplakia in 10 patients treated with brewer's yeast.

Hobaek (1946); Remove irritation by tobacco, sharp teeth, denture, improve oral hygiene. Radium treatment was used for cases showing gross atypia histologically, and electrocoagulation for uncomplicated cases.

Sharp (1948); Treatment should be conservative. Irritants should be removed. For the generalized type, hormone therapy was advocated.

Schork (1948); A programme of eliminating spices, spirits, tobacco, and supplementing the diet with Fleishmann's 20-40 yeast was found to control, if not completely eliminate, clinical leukoplakia. If syphilis was present, biopsy was also needed.

Ward and Hendrick (1950); Advised removal of chronic irritants, and recommended irradiation. Vitamin A, 100,000 units daily for months, gave some success.

Schaffer (1952); Irritants should be removed. Excision is more effective than radiation, but both may be used.

Madden (1952); Found vitamins A and B of little value.

Howell (1952); Recommended a "sharing operation" in recurring leukoplakia of the lower lip.

Salman and Langel (1954); If uncomplicated, observe periodically, remove irritation. If verrucous, papillary, or fissured, biopsy should be taken. Small patches can be removed by high frequency current or electrodesiccation. Larger patches may be removed by x-ray or radium.

Boyle (1955); In early stages, leukoplakia may be arrested by elimination of irritation. Later, if small, it may be excised surgically. Tobacco and sources of irritation should be removed. No caustics should be applied.

Cheraskin and Langley (1956); Eliminate local irritants. This may lead to regression and return of normal tissue. Bland mouth-washes and nonabrasive diet may aid in reducing trauma. In isolated cases, the use of vitamins A and B and oestrogen may aid in the recovery. In extensive and intractable instances, electrodesiccation or surgical excision is utilized.

Sharp et al (1956); The best treatment is excisional biopsy. If the condition is generalized, any localized change makes a biopsy imperative, and appropriate treatment instituted. If the irritating factors can be determined and eliminated, the condition may be arrested or disappear completely. If not, excision is recommended,

with repair by sliding mucosal or split-thickness skin grafts, unless regular follow-up observation is possible.

Shira (1957); Advises complete removal of clinically diagnosed leukoplakia (showing dyskeratosis).

Sutherland (1959); 1. Remove local irritation, 2. Perform biopsy, 3. Keep under review.

Bernier (1959); For pachyderma oris - up to 2 to 4 cms. in size, surgical removal in toto is recommended. If dyskeratosis is absent, it is possible that recession may occur following local measures such as the administration of large doses of vitamin B or of stilboestrol. Larger lesions present additional problems. Even if one could be sure of the changes operating in all parts of the lesion, it is possible that surgical removal would be too difficult to attempt. Palliative procedures are indicated. Smoking, alcohol and condiments should probably be eliminated.

For leukoplakia (showing "dyskeratosis"); Removal of the lesion through surgery, electrodesiccation or endothermy is the treatment of choice. Small lesions may be removed by excision biopsy. In larger lesions, complete elimination is difficult, but it is probably better to attempt actual surgery, employing a "stripping" technique in stages. When on the lip, "lip shave" is effective. All local irritations must be eliminated.

Thoma and Goldman (1960); 1. Elimination of factors of irritation, 2. Elimination of systemic factors, treatment of syphilis,

vitamin A therapy over an extended period of time, 3. Destruction of small lesions by electrodesiccation, 4. Treatment with oestrogenic hormone to produce desquamation, a method in the experimental stage, 5. Excision by endothermy of larger areas, if removal of the cause is ineffective, 6. Radiation, according to Sturgis and Lund, was ineffective.

Orban and Wentz (1960); For hyperkeratosis simplex; 1. Elimination of all possible local irritating factors, without compromise, 2. Systemic treatment (a) use of high vitamin therapy, especially A (150,000 units per day for months), (b) use of liver extract, vitamin B₂ and iron therapy if patient is anaemic.

For hyperkeratosis complex; 1. Removal of entire lesion by surgical methods, electrocautery, fulguration or desiccation, 2. Elimination of all local and systemic factors, 3. Roentgen radiation and radium treatment are not advised.

Bhaskar (1961); For pachyderma oris - If the cause is removed, the lesion should disappear in about three weeks; if not, it may be excised.

For leukoplakia (with dyskeratosis); Total excision, with a respectable margin of normal tissue.

Archer (1961); 1. Remove all irritation, 2. Carry out general physical diagnosis for syphilis, avitaminosis A, allergies, hypercholesterolaemia, excess oestrogen, 3. If the above measures are unsuccessful, biopsy should be taken. If nonmalignant, excise with radiosurgical loop. "Watchful waiting" is not advisable! If malignant, the lesion should be treated as such.

Burket (1961); Obtain patient co-operation, this being difficult at times. All traumatic and microbial sources of irritation should be eliminated, also tobacco, alcohol, highly seasoned foods. Vitamin B complex and C therapy may be used as a general supportive measure. If there is no dyskeratosis, vitamin A, topically applied for preference, may be administered for 4 to 6 months. Mulay and Urbach, and Burket, have used this method with encouraging results. Side effects are rare, but irritability, fretfulness, itching, fissuring at the corners of the mouth and bleeding of the lips may indicate chronic vitamin A intoxication. Gentle rubbing daily may be helpful. The more simple hyperkeratotic lesions frequently undergo dyskeratotic changes, so rebiopsy after 6 to 12 months is often indicated.

If dyskeratosis is present, surgical excision of moderately sized lesions should be performed. If extensive involvement is present, "stripping" is indicated.

Hyperkeratotic areas on the palate may benefit from coverage by a denture. In the case of mandibular dentures on hyperkeratotic areas, placement is not advised.

Brown (1962); This case report describes leukoplakia of the lip treated by "lip shave". In dealing with precancerous lesions, it is a much better procedure to remove the entire growth in toto, rather than leave it undisturbed or to treat it conservatively after receiving a biopsy report which is negative for evidence of malignancy.

Smith (1962); Massive buccal vitamin A doses were used in the treatment of hyperkeratotic lesions occurring on the oral mucous membranes. Good results were obtained in those lesions that were considered minimal, and fair results were obtained in those lesions in which histological changes were considered moderate. In all cases, the oral health of the patient showed varying stages of improvement. The vitamin A therapy produced no improvement when the lesions were considered dyskeratotic and irreversible. Less than 1% of the lesions regressed after cessation of the vitamin A therapy.

Stones (1962); Any recognizable cause must be removed, and all factors likely to irritate the condition should be eliminated. Attention should be given to the diet. If the lesion persists, or histologic examination indicates that it is possibly precancerous, the lesion should be removed surgically if possible. Radiotherapy is rarely of value.

Shafer, Hine and Levy (1963); Elimination of irritating factors, such as tobacco, alcohol, correction of malocclusion, ill-fitting dentures, vitamin A, B complex therapy, oestrogens, x-ray therapy, pulguration and excision have been used. The correction of local factors is probably of greater benefit than treatment of possible systemic factors.

Relatively small lesions may be totally excised, or cauterized, though the possibility of "field cancerization" must always be considered. Extensive lesions are often treated by

multiple stage stripping procedures, with or without skin grafting. A stripping procedure, without grafting, for lip leukoplakia, is especially common, and successful. X-ray radiation should be discouraged.

Shira (1964); Excision biopsy whenever possible.

Relatively large areas can be removed by "stripping procedures". Known irritative and stimulating factors should be eliminated to obviate the possibility of a recurrence, and the patient periodically observed.

Where larger areas are present, biopsies should be taken from several areas. If the lesion is pachyderma oralis, remove irritants, and large doses of vitamin A and B complex, as well as hormone therapy may bring about regression. If the lesion is leukoplakia (showing dyskeratosis), a vigorous surgical approach to completely remove the entire lesion should be carried out by using a "stripping" technique in stages.

Some surgeons prefer to resort to electrosurgery, either desiccation or coagulation.

McCarthy and Shklar (1964); If there is evidence of dyskeratosis or early malignant alterations, the lesion is to be considered as an early preinvasive epidermoid carcinoma. Current therapy would involve surgical removal of the lesion with a reasonable margin of normal tissue. A "stripping" operation is preferred by many surgeons, and this operation is acceptable since the lesion is not invasive and does not penetrate deeply into

underlying connective tissue. Electrosurgery may be used. Radical surgery is not indicated. Radiation is contraindicated, as its effectiveness in treating leukoplakia is questionable, and the possible complications in relation to mucosa and bone may be considerable. The patient must be warned against smoking and all oral irritation. Obviously, he is a susceptible individual and will again develop leukoplakia or carcinoma if the mucosa is irritated.

If there is no evidence of dyskeratosis microscopically, the lesion may be considered a simple response to irritation of the oral mucosa. Therefore, surgical removal is not necessary. All irritants should be removed - sharp teeth, ill-fitting appliances; smoking. Cessation or even reduction of smoking often results in disappearance of the leukoplakial lesion.

Vitamin A therapy, based on animal experimentation, has not proved of value, and keratotic lesions in human beings resulting from vitamin A deficiency have not been demonstrated. Multivitamin supplements have not been found to be of value. Oestrogenic hormone may increase the resistance of the tissues to leukoplakial involvement in menopausal females, but this therapeutic approach is not suggested unless the lesions are particularly severe and widespread. The carcinogenic potentialities of oestrogenic hormone indicate its use only in situations of sufficient gravity.

The removal of local irritants must be of primary importance. There is no contraindication to placing a well-fitting denture over areas of palatal leukoplakia. In most cases, the leukoplakia will regress, provided it has been shown to be of the simple hyperkeratotic variety.

Summary;

1. Most recent authors are agreed that the management of leukoplakia depends upon microscopic diagnosis.
2. There seems to be general agreement that all possible sources of irritation should be removed, irrespective of the microscopic picture.
3. Most authors agree that where the microscopic examination discloses "dyskeratosis", the complete lesion should be removed wherever possible.
4. Where no "dyskeratosis" is disclosed, there is not unanimity on the need for removal, depending on whether the individual author regards a simple hyperkeratosis as being capable of transformation into a "dyskeratotic" one. This reviewer feels that where conservative treatment is undertaken over an extended period, biopsy should be repeated at frequent intervals, and should "dyskeratotic" changes appear, "stripping" procedures should be employed.
5. Recent authors seem to have swung away from the use of vitamin therapy. Considerable space has already been devoted, in this review, to the place of vitamin A in the aetiology of leukoplakia. Some further discussion will be entered into here, on its place in the therapy of leukoplakia.

Jolly (1964) quotes Moore as suggesting that we may consider that the epithelium, even in the absence of oestrogens, has a tendency to cornification unless it is stimulated by vitamin A to produce mucus, and so "according to this conception, cornification during

normal oestrus can be explained by interference in the action of vitamin A by the periodical accumulation of oestrogens".

Fell (1963, quoted by Silverman et al, 1963 VII) has demonstrated an antagonism between vitamin A and hydrocortisone in an organ culture system using the epidermis of chicken embryos. In attempting an explanation of this phenomenon, Fell states that studies indicate that basal cells and early differentiating cells in keratinizing epithelium have a mechanism for producing sulphated mucopolysaccharides. This mechanism, which is lost during keratinization, is not stopped in the presence of vitamin A. She speculates that lysosomal proteases are released which break down the precursors of keratin in the epithelial cells, and that certain steroids may inhibit the release of these hydrolases.

However, this is not an all or none response, for half of the patients in this study of Silverman et al (1963 VII) exhibiting partial remissions under vitamin A therapy were males, this trend being confirmed by other workers.

Silverman et al observed an increase in the number of mitotic figures in all specimens at the end of vitamin A administration. This is substantiated by the observations of Jolly, who found that a vast reduction occurred in the rate of mitosis in the oral epithelium of vitamin A deficient rats. The increases in mitotic figures suggested that there may exist a relation between the site of action of vitamin A on nuclei that are still mitotically active, epithelial renewal rates, and time needed during maturation for cornification to

take place. This supposition was indirectly supported by the observations of transformations of hyperpara- and hyperortho-keratosis to lesser degrees of cornification, which may be due to stimulation of mitotic activity and acceleration of epithelial turnover. On the other hand, there is much laboratory data indicating effects of vitamin A on various biochemical systems that may antagonize keratin formation.

Jackson and Fell (quoted by Silverman et al) have demonstrated electronmicroscopically that vitamin A on embryonic chicken skin in organ culture leads to a lack of density and disappearance of filaments in basal cells. These filaments, when present, coalesce to form tonofibrils, which are associated with keratin formation. They again suggest that vitamin A may inhibit the synthesis of this fibrous protein or catabolyze the fibres after synthesis by releasing cellular hydrolases. Silverman et al comment that at the present time, the differences in cornification of the various oral mucosal sites have been explained only by functional irritation. (This is not confirmed by this reviewer's reading of the literature). In studying four oral regions of a group of mice, Meyer, Medak and Weinmann have indicated a relationship between mitotic indices, growth rates and epithelial width.

Silverman et al make an incidental comment that, although biopsy specimens of hyperorthokeratosis give the appearance of the stratum corneum being an amorphous mass of protein, careful cytological scrapings indicate that most or all of the superficial cells

are still intact. This accords with the findings of Zelickson, who states that the cells are shed intact by dissolution of the cementing substance of the desmosomes.

Mercer's (1961) report of the experiments of Lasnitski, and Fell and Mellanby, makes it clear that the metaplasia of the basal cells resulting in the formation of mucus secreting cells was the result of changing the normal culture medium to one containing excess amounts of vitamin A.

It seems that the process of differentiation and production of keratin or mucin by the epithelium is a delicately balanced, physiological one mediated by vitamin A, hormones, and possibly other factors not yet elucidated. Everyone agrees that the thickening of the stratum corneum results from the application of a chronic irritant, but nobody can yet say with authority when this process becomes a pathological one and not a physiological one. The only yardstick possible at the present time, in the opinion of this reviewer, is regression of the lesion on removal of the stimulus, if one can be determined. If a thickened stratum corneum is the physiologic defence by the epithelium against the irritant, aborting that defence by inducing metaplasia towards mucin production through the administration of massive doses of vitamin A could hardly be considered desirable, rather it could be regarded as making the epithelium more vulnerable to the noxious stimuli, and so even predispose to neoplastic changes. Once the hyperkeratosis was deemed irreversible, and pathological in nature, there would be a more rational basis for the use of vitamin A, but even so, the

removal of the protective layer may not be advantageous, particularly if the absence of irritation could not be guaranteed. The metaplasia towards overall mucin production may, in the final analysis, produce an epithelium quite as abnormal as the hyperkeratinized one, without striking at the basic cause of the disharmony in the epithelium. This view may be substantiated by the finding of Silverman et al that within two weeks of discontinuance of vitamin A therapy, there was complete regression of the leukoplakic lesions, and by the finding of skin rashes and pruritis in previously normal skin during therapy. The latter effect probably would be direct, and not an allergic response. Further, in view of the association of increased and abnormal mitosis with the pathology of carcinoma, stimulating the mitotic rate above physiological levels by vitamin A administration does not seem advisable. Finally, the "remarkable" clinical finding of Pindborg et al (1963 V) of 29 "speckled" type leukoplakias (commissures 23, alveolar sulcus 4, buccal mucosa 2) in the buccal area, out of 35 such lesions (in a total of 185 leukoplakias) must prompt speculation as to whether these patients had been treated in any way previously. The report does not give this information.

Intake of adequate vitamin A, and plasma vitamin A levels, may not always be significant, liver dysfunction and adrenal activity both exerting an influence, and the only true criterion is whether the normal physiological balance is operating in the epithelium itself. Until this process is more fully elucidated, treatment by vitamin A must necessarily remain empirical.

If dietary analysis shows that the patient is deficient in vitamin A intake, the diet should be adjusted to bring this up to normal levels, and an attempt made to restore adequate nutrition. Present knowledge does not seem to confirm the value of massive doses. If the effect of buccal vitamin A is due to penetration from the external surface of the epithelium, as suggested by Silverman, Renstrup and Pindborg, several mechanisms could be suggested:-

1. Stimulation of the mitotic rate of the basal cells, thus slowing the rate of keratin formation.
2. Metaplasia of the basal cells, swinging them from keratin to mucin production.
3. Neutralization of the "inhibitor", which, according to Mercer, may be the restraining factor on cell division, then mechanism No. 1 would follow.
4. Acceleration of the process of exfoliation of cells, which seems to be determined by the nature of the cementing substance of the desmosomes.

In view of the severe xerostomia produced in vitamin A deficient rats as shown by Jolly, the possibility that the effect of vitamin A takes place through stimulation of the salivary glands to produce substances which then act on the mucous membranes, must not be overlooked.

The Incidence of Carcinoma in Leukoplakia.

Hagan and Eichenlaub (1922); Of ten patients with areas of leukoplakia, two developed cancer.

King and Hamilton (1931), quoted by Pindborg et al, 1963; 6.3% of 80 cases of leukoplakia showed malignancy on biopsy.

Sturgis and Lund (1934); Found that 12% of 298 cases of leukoplakia developed malignancy in five years.

Lain (1940); Of 82 cases of leukoplakia, two developed lip cancers. Biopsy was not taken, nor was the duration of observation given.

McKown From a statistical analysis of 100 cases of leukoplakia, found 30% of cases became malignant, after an average duration of 1.4 years.

Carr (1948); Reported a case where the initial diagnosis was leukoplakia, and four years later squamous cell carcinoma developed. The patient stated that the lesion had been present nine years before the first examination.

Schork (1948); Relatively few leukoplakic spots develop into carcinoma.

English (1949); Leukoplakia is significant as a precancerous lesion, mainly because it indicates the existence of chronic irritation.

Leonardelli and Tolamazzi (1950, in Pindborg, et al, 1963); 20% of 268 leukoplakias became malignant in from one month to fifteen years.

Boyle (1954); 37 dermatologic or dermatologic-like lesions were examined, 27 microscopically; 1 lesion was found to be malignant.

Boyle (1955); 20-30% of oral squamous cell carcinomas develop from pre-existing leukoplakic patches.

Bredy (1955, in Pindborg et al, 1963); 20% of 15 leukoplakias showed malignant or premalignant changes.

Sovadine (1955, in Pindborg et al, 1963); Of 55 leukoplakias 7.3% were premalignant, 7.3% malignant, a total of 14.6%.

Sharp et al (1956); 50% of patients with lip cancer had pre-existing leukoplakia, senile keratosis or cheilitis. In the cheeks, the figure is higher.

Fleming (1957); Described early carcinoma in a leukoplakic patch in right buccal mucosa, and uncomplicated leukoplakia of left buccal mucosa in the same patient.

Renstrup (1958); 100 patients with white lesions were observed for 16 months; 8 cases were lichen planus, 1 psoriasis, 1 could not be diagnosed. Of the remaining 90, clinical examination indicated 9 carcinomas, all being confirmed histopathologically.

Weisberger (1957); 22 patients with leukoplakia, diagnosed by microscopic examination, and without evidence of cancer, were closely observed for four years. At the end of this time, 8 patients had developed carcinoma at the site of leukoplakia.

Sugar and Banoczy (1959, in Pindborg et al, 1963); 6% of 86 leukoplakias became malignant over 11 years.

Skach, Svoboda, and Kubat (1960 in Pindborg et al, 1963); 1.6% of 71 leukoplakias became malignant over a period of 3-6 years.

Waldron and Shafer (1960); Quote a tabulation by Mackee and Cipollaro (1937) of the publications of 28 authors from the older literature which showed an average of 30% malignant transformation. The validity of such a high incidence might well be questioned based on more recent publications and their own experience.

Robinson (1957a); believes that only a small percentage of leukoplakias progress to carcinoma. He (1957b) further questioned whether the association of cancer and leukoplakia is really proven, and suggests that the profession has been over-zealous in diagnosis and the use of the term "precancerous".

Orban and Wentz (1960); These lesions (of hyperkeratosis complex - showing dyskeratosis) may represent a progression from milder hyperkeratosis simplex cases as the result of long-continued irritation, and possible modification by unfavourable systemic, hormonal, nutritional and genetic factors.

Shafer and Waldron (1961); 8.1% of 332 patients with leukoplakia were found to have carcinoma on histologic examination.

Hahn et al (1961, in Pindborg et al, 1963); 10% of 152 cases showed malignancy on biopsy.

Winiker-Blanck (1961 in Pindborg et al, 1963); 10% of 66 cases showed malignancy on biopsy.

Bhaskar (1961); 25% of leukoplakias (showing dyskeratosis) became malignant (These figures are hard to relate to other studies where dyskeratosis is not implied in the use of the term leukoplakia. Bhaskar does not say how many cases, if any, of pachyderma oris, progress to carcinoma - Reviewer).

Hellinger et al (1963); Of 45 cases of leukoplakia, 2 showed malignant changes.

Pindborg et al (1963); Of 185 cases of leukoplakia, 12.4% showed "epithelial atypia", 3.2% carcinoma, a total of 15.6%.

Summary.

The number of studies showing the percentage of Leukoplakic lesions which develop carcinoma is very small. The results vary up to 36% in this review. The actual percentage is not over-significant, as long as it is realised that leukoplakia does progress to carcinoma in some cases, making it essential for biopsy to be taken in all but the most transitory lesions.

The Incidence of Leukoplakia in Carcinoma.

Ullman (1935, quoted by Silverman et al, 1963); In 67 cases of carcinoma, 30% had associated leukoplakia.

Martin and Sugarbaker (1940); In 103 cases of cancer of floor of mouth, leukoplakia was present in 25%, in the tongue in 46%, and in the cheek in 70%.

Martin et al (1941); In 375 cases of lip cancer, found leukoplakia present on the lips, tongue and cheek in 28% of patients.

Schreiner and Christy (1942); In an analysis of 636 patients with lip cancer, there were 15 instances of leukoplakia, 197 histories of keratosis. No explanation of the histologic differentiation between keratosis and leukoplakia was given.

Hobaek (1946); Of 1,272 cases of oral cancer, 176 (16%) developed on the basis of pre-existing leukoplakia.

Archer and Morris (1946); In 203 patients with oral carcinoma, leukoplakia was present in 32 patients (15.8%).

Sharp and Spickerman (1947); In one group of 27 patients with lingual cancer, 40% had leukoplakia, while in another group of 54 patients, 37% had leukoplakia.

Bernier and Clark (1948); 40% of 330 cases of lip cancer had a secondary diagnosis of leukoplakia.

Cross et al (1948); 14.5% (82 cases) out of 563 patients with carcinoma of the lip also had leukoplakia.

McCarthy (1949); Leukoplakia precedes mouth carcinoma in one-third of all oral cases, one-half of tongue cases.

Weisberger (1957); Reports that 60% of 275 patients with oral carcinoma had leukoplakia adjacent to the area of cancer.

Wilkins and Vogler (1957); 40% of 81 cases of cancer of the gingiva had leukoplakia on some part of the buccal mucosa in addition to cancer. In many it seemed that cancer arose in an area of leukoplakia. 17% of the 81 cases had or developed one or more additional primary carcinomas. The frequency of leukoplakia in these patients was significantly higher than in those patients with one cancer. Of the 67 with one cancer, 21 (31%) had leukoplakia also, of the 14 with multiple primaries, 11 (79%) had leukoplakia also. These data suggest that a patient with one cancer and leukoplakia has a greater chance of developing another primary cancer in the mouth than the patient with no leukoplakia. This observation led them to believe that, in many instances, carcinoma of the mouth is the terminal manifestation of a chronically diseased mucosa.

Wynder and Bross (1957); Of 543 cases of mouth cancer, 19% also had leukoplakia. The two sites with the least history of leukoplakia were the tonsil and pharynx (4% each), and the highest the buccal mucosa, (45%).

Trieger et al (1958); 14.8% (16) of 108 patients with carcinoma of the tongue had leukoplakia.

Paymaster and Shraff (1959); Leukoplakia coexisted with carcinoma in 32% of cases.

Smith (1960); 19% (24) of 129 patients with cancer of the lips also had leukoplakia.

Meyer and Shklar (1960); found that 26% of a series of multiple malignant lesions of the oral cavity were associated with leukoplakial lesions.

Hayn (1961, quoted by Silverman et al, 1963); 62 patients with oral cancer showed leukoplakia in 11%.

Silverman et al (1963); 834 patients with oral cancer were studied, and leukoplakia also was found in 19%.

Summary.

These reports make it clear that it is impossible to determine the incidence of cases of leukoplakia which will undergo malignant transformation, and that the clinician cannot determine with any degree of certainty which cases of leukoplakia are potentially dangerous. Further, it must be noted that these reports refer to patients who already have carcinoma.

The average percentage of leukoplakia associated with oral carcinoma calculated from the preceding figures is 30. This figure

should be sufficient to convince the most sceptical observer of the potential for malignant change existing in mouths where there is leukoplakia, even though that observer may not be able to understand the exact process whereby that potential is established, and later realised.

Nevertheless, a most significant fact, and one that can easily be overlooked by those who are engrossed in the study of white lesions, is that an average of 70 per cent of oral carcinoma occurs with no white lesions presenting anywhere in the oral cavity. In these cases there has been no excess production of keratin, so that there is a reasonable doubt that the disordered production of keratin in white lesions is the significant change occurring as those lesions undergo neoplastic change. In fact, it could easily be argued that the white covering is protective and relatively favourable, as most authorities agree that carcinoma appearing in conjunction with leukoplakia usually does so after quite a long period, whereas carcinomas not associated with leukoplakia are usually described as having a shorter history. In nearly all cases it is a breach of the epithelium in the form of an ulcer (English, 1949), crack or fissure, that is, a disruption in continuity of the protective covering, which is described as heralding malignant change. Furthermore, lesions which build up above the surface are not considered as threatening as those where the surface layer is disrupted, unless there is a concealed fissure or ulcer.

To conclude this section I would like to quote Robinson (1957), "In raising this question, there is no intention to belittle the fact that leukoplakia is a warning sign indicating activity of an irritating factor that may be carcinogenic".

Leukoedema.

Leukoedema is an abnormality of the buccal mucosa which clinically resembles early leukoplakia, but appears to differ in certain respects. (As far as can be ascertained, this condition was first described by Sandstead and Lowe in 1953, and is reported by Shafer, Hine and Levy, and McCarthy and Shklar. Burket, using the term "leukoderma", states that the condition has been described as a disease entity by Sandstead and Lowe, and by Kollar et al.)

Aetiology.

The cause is unknown. The study by Sandstead and Lowe showed no apparent correlation between the incidence of leukoedema and the use of tobacco, the pH of saliva, oral bacterial infection, syphilis or galvanic irritation. The incidence was approximately 45% in white men, 40% in white women, 94% in Negro men, 86% in Negro women (all being adults with an average age of 45 years).

Clinical Features.

The gross appearance varies from a filmy appearance in the early stages to a more definite whitish-grey cast with a coarsely wrinkled surface in the later stages. Lesions occur bilaterally in the majority of cases and frequently involve most of the buccal mucosa extending on to the oral surface of the lips. It is most noticeable along the occlusal line in the bicuspid and molar regions. In some cases, desquamation occurs, leaving the surface eroded.

Histologic Features.

There is an increase in thickness of the epithelium, intracellular oedema of the stratum spinosum, an irregular, amorphous

surface without keratinization, and broad rete pegs which appear irregularly elongated. The characteristic oedematous cells appear extremely large and pale, and they present a reticular pattern. The cytoplasm appears lost, and the nuclei appear absent, clear or pyknotic. Inflammatory cell infiltration of the subjacent connective tissue is not a common finding.

Subsequent unreported studies by Stanley (quoted by Shafer, Hine and Levy) have shown that the white appearance of the lesions clinically is due not to spongiosis, but rather to parakeratosis.

Clinical Significance.

It has been suggested that leukoedema may represent a lesion of the oral mucosa in which leukoplakia is more apt to develop than in normal epithelium. This conclusion is based on the fact that nearly all patients examined who manifested leukoplakia also exhibited leukoedema in the adjacent mucosa. Since the aetiologies of both are not established, analysis of the relation of these two conditions must await further study.

CARCINOMA.

As this review is titled "White Lesions of the Oral Cavity", the discussion will be limited as far as possible to carcinoma occurring as a white lesion. Some other material will have to be presented so as not to provide a distorted picture of this important subject. Of necessity, the treatment of the subject will be brief, as it would be impossible to deal adequately with oral carcinoma unless it was treated as a separate study.

Oral carcinoma will be considered under the following headings:-

1. Biopsy,
2. Incidence,
3. Clinical Manifestations,
4. Symptoms,
5. Histopathology,
6. Aetiology,
7. Premalignant lesions,
8. Therapy,
9. Multiple oral malignant lesions,
10. Spread of oral carcinoma.

1. Biopsy.

Because of the great frequency of the occurrence of oral carcinoma, and its extreme clinical variability, carcinoma must always be considered in the differential diagnosis of lesions of the oral mucosa. If there is the slightest doubt clinically, a biopsy specimen must be obtained immediately.

An oral carcinoma is not "activated" by cutting into it for a biopsy specimen, nor is metastasis facilitated. Whether cancer cells which settle in new areas grow is related to the differentiation of the cell and the "preparation" of the site, (McCarthy and Shklar, 1964). The risk of spreading is far outweighed by the danger of not obtaining an early diagnosis.

If the oral cancer is large and ulcerated, biopsy is unnecessary and useless, and the patient should immediately be referred for therapy. Most writers consider the dentist qualified for biopsy-taking, but Gade and Lee (1957) stated that only the person who is prepared to undertake treatment should perform the biopsy.

Dingman (1948 & 1949), and Sharp et al (1956) give excellent accounts of the technical procedures involved in biopsy.

The importance of biopsy in leukoplakia has already been stressed.

2. Incidence.

- (a) General. Tiecke and Bernier (1954) stated that oral carcinoma caused 3% of all cancer deaths, while Sharpe et al (1956) aver that oral carcinomas make up 5% of all

cancers. Cahn and Slaughter's figure is 4% of all cancers, and that of McCarthy and Shklar, 10%.

- (b) According to Sex. The male:female ratios, given by various authors, are as follows:-

Archer and Morris (1946) 85:15; Cross et al (1948) 98:2 (for cancer of the lip); English (1949) 87-90% males; Ward and Hendrick (1950) 97:3 (lips); Tiecke and Bernier (1954) 96:4 (mostly army personnel); Sharp et al (1956) 85:15; Bucalossi and Ristro (1957) 84:16 (tongue); Tiecke (1957) 85:15 (tongue and floor of mouth); Wilkins and Vogler (1957) 46:54; Wynder and Bross (1957) varies from 2:1 to 10:1 for different sites; Trieger et al (1959) 87:13; Pinsonneault and Gill (1960) 97:3; Castigliano (1961) varies from 98:2 in the lip to 10:1 on the tongue and palate; Dunn, (1962) 65:35.

Although there is some variation according to site, it is obvious that oral carcinoma is predominantly a disease of males, with a general ratio of about 8:2.

- (c) According to Age. The age incidence figures according to various authors are as follows:-

Ewing (1940) 36-60; Archer and Morris (1946) 78% between 45-74; Cross et al (1948) average age 62 (lip); English (1949) average age 45-60; Ward and Hendrick (1950) average age about 60 (lips); Tiecke and Bernier (1954) 55; Sharp et al (1956) about 60; Bucalossi and Ristro (1957) 62 (tongue); Tiecke (1957) 55 (tongue and floor of mouth);

Wilkins and Vogler (1957) 39-80 years, 50% women were less than 60, 30% men less than 60; Trieger et al (1959) average age for men 57, for women 52, for those with cirrhosis of liver, average age 57, without cirrhosis, 70; Castigliano (1961) 63; Gardner et al (1963) 52.5.

It will be seen that the average age in all studies is about 55 years.

(d) According to Site. The following Table gives various authors' percentage figures of incidence according to site:-

Author	Buccal Mucosa	Floor of mouth	Tongue	Palate	Alveolar mucosa	Lip	Tonsil
Tiecke and Bernier(1954)	9	16	52	11	12	Not Included	
Sharpe et al (1956)	5	7	20	5	12	51	
Bucalossi and Ristro (1957)			25				
Castigliano (1961)	11	9	24	7	14	25	8
" "	3.2	3.5	23.9	15.5	5.4	36.5	12.0
Southwick et al (1961)		52.					
Gardner et al (1963)	6.7	19.5	30.9	5	3.6	15.1	14.1

It is evident that the lip and tongue are the most frequent sites of carcinoma. This contrasts with leukoplakia, where the buccal mucosa is considered the most frequent site. This could in part be accounted for by the fact that many writers describe the precancerous lesions of the lip as "keratosis". Clinically, because these lesions

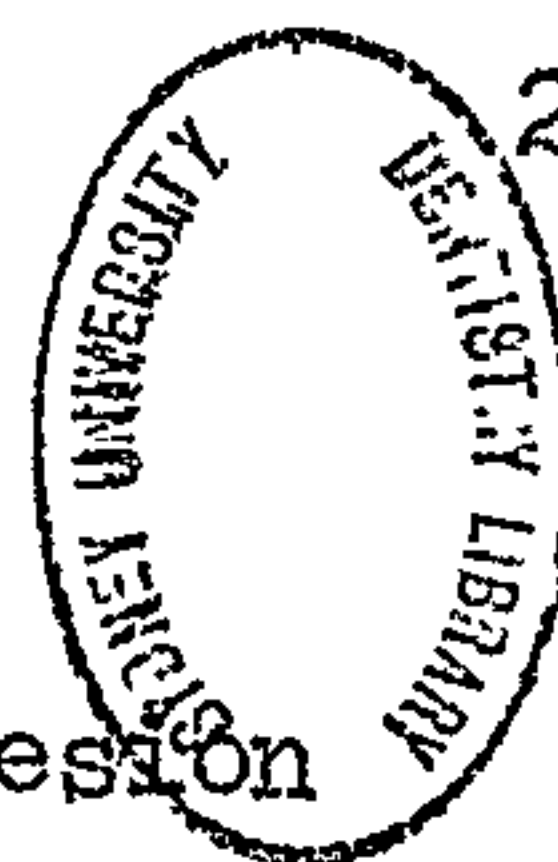
are not moistened by saliva, they do not have a white colour, but the microscopic picture seems to be very similar to that of leukoplakia. There probably is a genuine discrepancy however, which is explained by the effect of sunlight and pipe smoking.

The other features of incidence are so similar to those of leukoplakia, that the suggestion by Sharp et al (1956) and Wynder et al (1957) that the same factors that are important in the aetiology of oral cancer are operable in the aetiology of leukoplakia, appears very pertinent.

3. Clinical Manifestations.

The clinical manifestations of carcinoma are extremely varied, and numerous descriptions of the lesions are found in the literature, but it is thought that a representative description by McCarthy and Shklar (1964) will be adequate for this review;

- (a) Papillary or Verrucous type; This type of lesion is an exophytic growth and is seen as a papillary mass of varying size, with a broad base or a relatively narrow pedicle. In carcinoma, the base tends to be broad and the margins of the lesion somewhat indurated. The papillary mass appears pink or red and may present some surface ulceration in larger lesions. The surface texture of the raised mass may be pebbled, verrucous, or relatively smooth.
- (b) Ulcerative type; This type of lesion appears as a discrete ulcer with a raised indurated margin, or as a relatively large area of ulceration with firm indurated tissue at the periphery.



- (c) Deeply infiltrating or scirrhous type. This type of lesion invades deeply into underlying tissues but presents relatively little surface manifestations. The area is firm and hard. There may be some surface ulceration or tissue proliferation. The area may be slightly raised. This type is fortunately uncommon, since the demarcation of the lesion is difficult to assess, and the absence of surface manifestations often results in the lesion first being diagnosed in an advanced stage.
- (d) Leukoplakic type; The premalignant variety of leukoplakia eventually gives rise to carcinoma, and initially the clinically picture does not alter, although the microscopic features have progressed from dyskeratosis to malignant neoplasia. Gradually the leukoplakic area is replaced by a proliferation or ulcerative and expanding lesion.

As an oral carcinoma progresses, the pattern becomes more irregular, and surface trauma and infection invariably complicate the carcinoma.

4. Symptoms.

The symptoms of oral carcinoma are of little clinical significance. The lesions are not painful, unless ulcerated and infected, and in this condition are not more painful than other oral ulcerations of a nonneoplastic variety. The pain of an aphthous ulcer is infinitely greater than that of a carcinoma of the oral mucosa.

Lesions of the tongue tend to cause some abnormalities of

function. The patient may complain of speech difficulty, there may be glossopyrosis, and abnormalities of taste sensation.

5. Histopathology.

Other than in the standard dental pathology textbooks, one rarely finds descriptions of the histopathology of oral carcinomas, and in these sources, the descriptions appear to be fairly uniform. Therefore the following description has been adapted from Shafer, Hine and Levy (1963):-

In general, oral carcinomas tend to be moderately well differentiated neoplasms with some evidence of keratinization. Highly anaplastic lesions do occur, but are more rare; they metastasize early and widely and cause death quickly.

The well differentiated carcinoma consists of sheets and nests of cells with obvious origin from squamous epithelium. The cells are generally large, with a distinct cell membrane, but inter-cellular bridges may be absent. The cell nuclei are large, show variable staining intensity, some being hyperchromatic. Mitotic figures may be found, but are not very numerous, and many of these are atypical. A prominent feature is individual cell keratinization, and the formation of numerous epithelial or keratin pearls of varying size. Groups of these malignant cells can be found actively invading the connective tissue in a vagarious pattern. Less well differentiated carcinomas become less pronounced in their resemblance to squamous epithelium. The shape of the cells and their typical arrangement to one another may be altered. The growth rate of individual cells is

more rapid, resulting in more mitotic figures, greater variation in size, shape and staining, the lack of keratin production.

The poorly differentiated carcinomas bear little resemblance to their cell of origin, and often will present diagnostic difficulties because of the primitive and uncharacteristic histologic appearance of the malignant, rapidly dividing cells. These cells show an even greater lack of cohesiveness and are extremely vagarious.

The recognition that different degrees of differentiation occur in the carcinoma prompted Broders to suggest a grading system in which a grade I lesion was highly differentiated (producing much keratin) while grade IV was very poorly differentiated (with highly anaplastic cells and practically no keratin). The fact that the same tumour may show varying differentiation in different areas has prompted the discontinuance of the grading system. Instead, most pathologists now modify the diagnosis of the neoplasm by a descriptive adjective indicative of its differentiation. Thus an indication can be given to the clinician of the nature and probable future behaviour of the lesion.

Kollar et al (1954), Thoma and Goldman (1960), Castigliano (1961), Bernier (1957 & 1959) and Topazian (1961) used the Broder's system, while McCarthy and Shklar (1964) now use the descriptive grading.

Metastases from intraoral carcinomas of different sites involve chiefly the submaxillary and superficial and deep cervical glands. Occasionally, other nodes such as the submental, preauricular

and postauricular nodes and supraclavicular nodes may be involved, but blood stream metastasis from oral cancer is uncommon. Tiecke and Bernier (1954) however, reported distant metastases in 22% of 195 patients who had died of oral carcinoma, the lung being the most common site; and Topazian (1961) confirmed this by demonstrating 24% distant metastases (75% to the lung) in 83 autopsies.

Burstone (1961) has given the following picture of histochemical reactions in oral cancer:-

Acid phosphatase is increased, while Burstone quotes Gomori as stating that 90% of all malignant epithelial tumours show very high activity. In some sites dyskeratotic cells show considerable esterase activity, and various authors have linked the increase in aminopeptidase activity with the invasive activity of cancer. Cytochrome oxidase is decreased.

Oka et al (1964) studied resected neoplastic tissues of the oral cavity histochemically and found that B-glucuronidase activity was confined to the cytoplasm of both neoplastic and non-neoplastic cells.

McCarthy and Shklar (1964) found the "basement membrane" intact around cell nests of well-differentiated carcinomas; by the use of pa - S staining.

6. Aetiology.

As the aetiology of carcinoma so closely parallels that of leukoplakia and is of such importance and relevance in a discussion of white lesions, it will be given rather full consideration.

Erich (1948); Exposure to sun and chronic irritation from tobacco are the most common contributing causes of carcinoma of the lip.

Cross et al (1948); mention as significant for cancer of the lip, age, male sex, presence of positive Wassermann test 7.2%, tobacco (335 of 563 patients were habitual users, of these 71% were pipe-smokers), trauma (62 patients had a history of repeated trauma, 41 of these also having poor oral hygiene), 14.5% associated with leukoplakia.

Lyman (1948); Injuries caused by various dental conditions are apt to start a sequence of changes within the oral tissue which may terminate in malignant degeneration.

Martin (1948); Leukoplakia and carcinoma have a common aetiology as far as chronic irritation is concerned. The significance of dental irritating factors has been greatly over-emphasized.

Sharp (1948); For lip cancer, chronic irritation is important. Exposure is the major factor, sensitive skins predisposing. Chemical and thermal irritants, repeated trauma, dental factors, are important. Constitutional disease (syphilis) is a minor factor. Underlying is the individual predisposition.

Woodbury (1948); Chronic irritation from smoking, sharp teeth, fillings, dentures, syphilis, sun and wind.

Balendra (1949); High incidence of buccal carcinomas in betel nut chewers in India is due to (a) attrition, malocclusion, sharp edges producing ulcers, irritation by the chemical products of the quid, and (b) insufficient vitamin A in the diet.

Ward and Hendrick (1950); For carcinoma of the lip, exposure to sunlight is important, but not smoking. Repeated trauma is significant. Syphilis may be a precursor, and confusion between the conditions may lead to a delay before treatment is begun.

Cutter (1953); mentions smoking, syphilis, poor oral hygiene, galvanism.

Schucknecht et al (1953); 1. Cigar and pipe smoking, 2. Mechanical trauma, 3. Systemic diseases - nutritional deficiencies (vitamin B) and syphilis (4% male population has syphilis, 30% with cancer of the tongue).

Pinkerton (1951); Malignant cells contain self-propagating particulate agents which are passed from cell to cell in mitotic division, and are the cause of abnormal behaviour. They may be formed by mutation of normal cytological constituents, or may be set into action from a dormant state, when cells are acted on by a carcinogen.

Tiecke and Bernier (1954); The significance of tobacco is not clearly established; syphilis seems to be significant (18% had syphilis in their study compared to 5% in general population); leukoplakia (with dyskeratosis) was not seen in their study, while trauma - dental trauma, etc, are mentioned. The significance of heredity could not be determined.

Cheraskin and Langley (1956); Predisposing factors are; 1. Chronic irritation, 2, Nutritional deficiencies, 3. Exposure to carcinogens such as X-rays and radium.

Sharp et al (1956); For lips; sunlight, dietary deficiencies (vitamin A, B. protein), systemic predisposition (including syphilis), smoking. For other areas, the same factors, excluding sunlight, and adding chronic trauma, sepsis and dental irritations.

Berridge and James (1956); Suggest that poor oral hygiene and trauma are now playing a more important part than smoking in predisposing towards carcinoma. Syphilis is a significant predisposing factor only in anterior two-third of the tongue.

Cade and Lee (1957); For cancer of the tongue; the fall of the male rate in the last 30 years may be due to the rarity of gross leukoplakia associated with syphilis. The Plummer-Vinson Syndrome is common in Scandinavia, and associated with a higher lingual cancer rate there. There are some families with a cancer history.

Bucalossi and Ristro (1957); For cancer of the tongue, tobacco, traumatism, leukoplakia, papillomatosis and syphilis.

Tiecke (1957); For cancer of the tongue; there is an unknown primary factor, secondary factors are trauma, syphilis, tobacco, leukoplakia, carbon compounds and azo dyes. The effect of syphilis is not due to the organism per se, but to resultant ulceration and lowered resistance.

Kreshover and Salley (1957); Predisposing factors; avitaminosis A (sometimes associated with achlorhydria) and B, chronic alcoholism affecting nutrition. Vitamin B deficiency may affect the oxidative ability of the epithelial tissues. Syphilis is significant in tongue lesions, and galvanism may produce

leukoplakia. Sunlight is important for lip cancer. Roffo showed that excess cholesterol speeded the development of leukoplakia in experimental animals. Nathanson and Weisberger treated leukoplakia successfully with oestradiol.

Ziskin (1941) had previously demonstrated a keratogenic and proliferative effect of both oestrogen and testosterone on the gingiva of monkeys and humans. Nutlay et al (1954) confirmed this observation in old mice, but failed to show epithelial changes in young and growing animals.

Kreshover and Salley found that areas of the hamster mouth protected by saliva did not develop lesions, but the buccal pouch, and the ear, did so, when carcinogens were applied. Vitamin A and B deficiency accelerated the changes.

Toto (1957); For carcinoma of the gingiva - chronic irritation predisposes to both leukoplakia and carcinoma.

Halperin (1957); For carcinoma of the palate. Different people respond in different ways to the irritation of pipe smoking, cigar smoking, scalding liquid foods, and these variations may be the result of the time factor or of intrinsic susceptibility. Nutritional deficiencies and hormonal imbalance (associated with ageing) may be significant.

Wilkins and Vogler (1957); Smoking and chewing tobacco seemed to be a factor in males, and snuff-taking in females. 40% had leukoplakia, and this seemed to predispose to multiple primary growths.

Wynder and Bross (1957); See under aetiology of leukoplakia.

Bernier (1959); Gingival carcinoma is usually preceded by long-standing leukoplakia resistant to treatment.

Paymaster and Shroff (1959); In 700 cases of lingual carcinoma, syphilis was present in 10%.

Trieger et al (1959); Tobacco - 66 of 68 smoked 20 or more cigarettes daily; alcohol - 51 were habitual or excessive drinkers; syphilis - was present in 6, of whom 5 had alcoholic cirrhosis of the liver; oral irritants - 70% had definite evidence of long-standing irritation.

Hepatic disease - 40 (59%) had unequivocal evidence of hepatic cirrhosis, while 6 others had some history of liver dysfunction.

Combination of factors - multiple factors existed in 59 (87%). Of the group with multiple factors, 97% smoked to excess, 75% drank to excess.

The average age of developing carcinoma was 13 years higher in the absence of cirrhosis. The 5-year survival rate was 19% where cirrhosis was present, 40.3% if no cirrhosis was present.

Dalitsch (1960); Mechanical irritation, vitamin deficiencies, smoking are significant.

Dargent et al (1960); Dental irritation was more important than smoking. Their studies indicated a decrease in the incidence of lingual cancer in male patients over 60 years without a decrease in smoking; while in females, lingual cancer increased after 60 years of age.

There has been a decrease in the general incidence of oral carcinoma in France, due to the decrease in the incidence of syphilis, better dental and general health, and to a decrease in alcoholism.

Thoma and Goldman (1960); Intrinsic factors - varying susceptibility and slight hereditary tendency are present.

Extrinsic factors - all forms of chronic irritation, including heavy smoking.

Enzymatic factors - These authors quote Pinkerton (1951); "It seems likely that the cancer problem may eventually be solved by studying phenomena which are concerned with selective enzymatic inhibition, and the host-parasite relationship, if we can use the latter in its broadest sense". Betel-nut cancer was mentioned, with the views of Balendra. Leukoplakia, syphilitic hyperkeratosis, and senile keratosis are to be regarded as precancerous lesions if dyskeratosis is present.

The precancerous nature of hyperplasia of the gingivae, papillomas and other benign tumours is discounted. Atrophy of the mucous membrane is a predisposing condition in the Plummer-Vinson syndrome, occurring in women past middle age. It is characterized by atrophy of the mucosa of the mouth, tongue, upper gastrointestinal tract, and marked nutritional deficiency.

Odontogenic cysts have given rise to squamous cell carcinoma in rare cases.

Robinson (1962); Predisposing factors may be heredity, nutritional deficiencies, tobacco in certain persons, syphilis, hormonal imbalance, and four types of irritation; traumatic, thermal, chemical and radiation.

Age leading to a decrease in salivary flow may predispose to irritation, or underlying metabolic changes may predispose tissues to changes. Dental factors are rough teeth, fillings, ill-fitting dentures.

Castigliano (1961); The remote and fundamental cause remains unknown. Predisposing causes are - chronic irritation, solar rays (in the case of lip cancers), tobacco (through direct contact), smoking - the significance is not clear, syphilis is a factor in carcinoma of the tongue, in some cases of cancer of the lip, floor of the mouth, and buccal surface. Nonluetic leukoplakia is precancerous, but the chances of carcinoma are less than in the luetic type. Verrucous hyperplasias and oral papillomata should be regarded as precancerous. Dental factors are significant, but galvanism is not. Plummer-Vinson syndrome seems to be a factor in Sweden, but not in the U.S. There may be a lack of protective factors, possibly hormones. The incidence is higher in lower income groups. Chemical carcinogens, X-ray and radium play a part in the aetiology.

Renstrup et al (1961); When mechanical irritation was used in addition to the application of carcinogens, cancer was produced much more quickly. They were not able to determine how this happened.

Dunn et al (1962) believe that there is more than a casual relation between tobacco habits and carcinoma of the oral cavity, pharynx and larynx. With pronounced increase in smoking that occurred during and after World War II, an increase of carcinoma in oral cavity and upper respiratory tract probably will occur. As 30-40 years of smoking is usually a prerequisite, the peak has yet to come. The study was of 112 patients with carcinoma of the oral cavity, nasopharynx and larynx. 100 were smokers, 3 chewed tobacco, 6 used snuff,

5 did not use tobacco; 8 smoked cigars, 2 pipes, and the rest cigarettes.

Of 3 tobacco chewers, (also heavy smokers) 2 had buccal carcinomas, 1 carcinoma of the tonsil.

Of 6 snuff-takers, 5 had carcinoma of the floor of the mouth and alveolar ridge, 1 of palate and alveolar ridge. All of these were women, average age 69, who began the habit in their teens.

Of 5 non-smokers, 3 were related to chronic local irritations.

Of 15 with tongue carcinoma, 14 were smokers.

Of 16 with floor of the mouth and lower ridge carcinomas, 16 were smokers.

Of 4 with buccal mucosa carcinoma, 4 used tobacco.

All of 11 with carcinoma of the tonsil, 7 with carcinoma of naso-pharynx, 5 with carcinoma of the pharynx, 6 with carcinoma of the pyriform sinus, used tobacco.

Of 45 with carcinoma of the larynx, 45 used tobacco.

Of 3 with carcinoma of the hard palate and the upper alveolar ridge, 2 used tobacco.

Shafer, Hine and Levy (1963); Environmental factors are:-

1. Tobacco, 2. Alcohol, 3. Syphilis, 4. Nutritional deficiencies,
5. Sunlight (in the case of lip cancer), 6. Miscellaneous factors, including heat, particularly heat from a pipe stem in cases of lip cancer, trauma, sepsis, and irritation from sharp teeth and dentures.

There is now sufficient evidence to indicate that "field cancerization" actually does occur, and many patients with oral

cancer do have multiple, anatomically separated lesions at the same time or at intervals.

Cahn and Slaughter (1962); Mouth cancer is most often seen in association with poor oral hygiene and neglected teeth. This is particularly true of cancer of the lateral border of the tongue. Ill-fitting dentures may have a definite influence. Betel-nut and tobacco chewing present more obvious evidence of "local irritation". Tobacco smoking seems to be indicted.

Predisposing factors may be syphilis (in tongue cancer), cirrhosis of the liver, avitaminosis, atrophic glossitis arising from pernicious anaemia and the Plummer-Vinson syndrome.

"Field cancerization" is also mentioned.

Silberman and Shklar (1963); 1. In a series of young hamsters, the application to the buccal pouch of 0.5% D.M.B.A. and 1% croton oil resulted in a retardation of carcinogenesis when compared to the application of 0.5% D.M.B.A. alone. 2. In older Syrian hamsters the application to the buccal pouch of 0.5% D.M.B.A. and 1% croton oil resulted in an enhancement of carcinogenesis when compared to the application of 0.5% D.M.B.A. alone.

The application of croton oil resulted in more inflammation in younger animals, and Silberman and Shklar suggest that this may have resulted in the retardation of the carcinogenic action of D.M.B.A.

Salley (1963), basing his opinion on his experimental work with mice and hamsters, thought that, in the oral epithelium, smoke is a cancer-producing agent by chronic irritation.

Listgarten et al (1963) state that the major alterations in intercellular relationship and cell structure brought about by topical applications of D.M.B.A. to the hamster cheek pouch, that is, desmosomal disruption and peripheral clumping of the tonofibrils, are not unique to this tissue, and have been previously described in skin treated with D.M.B.A. Their finding is that widening of the intercellular spaces of the epithelium occurred at least as early as the second day of painting, suggests that a "portal of entry" may develop at the ultrastructural level, and indeed, may be brought about even by manipulation of the pouch.

Protzel et al (1964) found that; 1. Induced liver damage in mice decisively decreased the latency and increased the frequency of oral tumour development.

2. The role of induced liver damage on oral tumour development was related to its interference with benzpyrene metabolism.

3. It is possible that alcohol plays a dual role; (a) as a promoter or cocarcinogen with tobacco smoke on the exposed mucous membranes, (b) as an agent which interferes with the metabolism of a carcinogen in the hepatobiliary system.

Smith (1964), experimenting with hamsters, demonstrated that (1) the distribution and morphology of epithelial lysosomes altered conspicuously during carcinogenesis, (2) alterations in lysosomes, confined exclusively to the basal cells, were identifiable prior to histological evidence of malignancy, (3) the lysosome patterns of experimental carcinoma resemble those seen in human carcinoma, (4) the examination of lysosomes could possibly be developed to assist in the positive identification of malignancy.

Keller and Terris (1964) carried out studies of 700 males with cancer of the tongue, floor of the mouth, mesopharynx, hypopharynx and adjacent oral sites.

Smoking was more frequent among cancer patients by site groupings than their matched controls. This was true for tongue cancers and mouth-floor cancers. A strong association was found between liver cirrhosis and cancer of the floor of the mouth. These were uncommon among Jews, in contrast to Catholics and Protestants. All cancers were common among service workers and labourers. The association of liver cirrhosis and floor-of-mouth cancer is confirmed, while the paucity of these cancers and heavy alcohol consumption among persons who are Jews by religion is quite marked. The role of tobacco usage appears to be related to alcohol consumption in association with these cancers.

Oka et al (1964), studying surgically resected human neoplastic tissues of the oral cavity, found that B-glucuronidase activity was confined to the cytoplasm of both neoplastic and non-neoplastic homologous cells. Tumour parenchyma generally reacted more intensely than homologous healthy tissue, and proliferating connective tissue fibres and collagen bundles accompanied by inflammatory reaction showed an intense B-glucuronidase reaction; necrotic areas also showed a marked reaction.

McCarthy and Shklar (1964); The underlying tissue alteration is a fundamental cellular transformation which is maintained in successive lines. This may be either a true mutation with

alterations in the nuclear chromosomal structures, or perhaps a transmissible change in cytoplasmic structures such as the mitochondria. The mutation concept is supported by the work of Strong and others who have correlated the carcinogenic and mutation-inducing properties of various chemical substances in some types of organism. Cytoplasmic alteration is postulated by Warburg who indicates the mitochondria as being the site of a major transformation in the cellular metabolism, a change that is transmissible through successive cell lines. Malignant cells present a diminution in respiratory enzymes such as cytochrome oxidase, and Warburg has indicated that the fundamental transformation from a normal to a malignant cell is a biochemical alteration consisting of a gradual change from oxidation to fermentation with its characteristic energy deficiency. Respiration and fermentation are energy-producing reactions, synthesizing the energy-rich adenosinetriphosphate through which the energy of respiration and fermentation is then made available for life. Warburg envisions the morphologic cellular alterations as a response to the primary metabolic change, with highly differentiated body cells converted into wildly growing undifferentiated cells. The mutation concept would consider the altered cellular morphology and metabolism as manifestations of a basic chromosomal change, the altered genetic material then being passed on to all subsequent cells following mitotic division.

The production of malignant tumours can be carried out simply and routinely in experimental animals by the use of specific

chemical agents referred to as "chemical carcinogens". These tend to be polycyclic hydrocarbons and are capable of eliciting a tissue response by injection or by surface application. One commonly used is known as D.M.B.A. The work of Salley (1954) facilitated the study of experimental mucous membrane lesions, by finding that the hamster buccal pouch was an ideal site for the production and study of malignant lesions of the mucosa. It has been subsequently demonstrated that chronic irritation together with the use of a topically applied carcinogen will hasten the development of malignant tumours. It has also been shown that malignant lesions of the buccal pouch are preceded by a hyperkeratotic and dyskeratotic lesion, similar to the leukoplakia seen in human beings, and that this leukoplakic lesion is characterized by metabolic features similar to those of carcinoma (Santis et al, 1964). Thus, experimentally, mucosal carcinoma can be produced by carcinogenic substances, and can be produced more rapidly by the use of associated irritants.

Chronic Irritation; It is now generally accepted that the primary and most important aetiological factor related to the development of oral cancer is chronic irritation. Examples are; jagged teeth, a hot pipestem held continuously on a given area of the lip. The development of a carcinoma is often preceded in these cases by a premalignant zone of leukoplakia. Warburg suggests that intermittent irritation leads to intermittent circulatory disturbances and intermittent oxygen deficiency. It has been demonstrated experimentally that oxygen deficiency as well

as respiratory poisons such as urethane are capable of inducing neoplastic lesions.

Heredity; The degree of susceptibility or resistance to oral cancer is presumably determined by hereditary or genetic factors. Cancer-susceptible and cancer-resistant strains of mice have been bred, but hereditary factors in human beings are somewhat more complex. It has been found that certain families have a greater tendency toward the development of oral cancer. Meyer and Shklar (1960) found that, of a group of 768 cases of oral cancer, 4.7% developed multiple separate oral lesions and 2.4% developed malignant lesions of the mouth and gastro-intestinal tract. This would appear to indicate a general tendency toward the development of mucosal carcinoma in certain persons.

Sex; About 90% of carcinomas of the oral mucosa occur in males. The reason for this has not been clarified. The explanation of smoking in the male is untenable in view of current statistics. The female hormonal balance may serve to protect the oral mucosa, or perhaps the genetic background may account for this distinct sex difference.

Weathered and Salley (1964), experimenting with hamsters, suggest that oestradiol decreases the induction time of experimentally induced carcinoma of the oral mucosa, and that castration prolongs the induction time.

Predisposing Conditions; Plummer-Vinson syndrome, syphilitic glossitis, avitaminosis B, hepatic dysfunction.

McCarthy and Shklar summarize by stating that the aetiology

of oral carcinoma appears to be related to a variety of factors acting at different levels. (1) Hereditary and sex predispositions, (2) Predisposing degenerative alterations of the oral mucosa, preparing a favourable soil, (3) Exciting factors such as chronic irritation, (4) Possible chemical carcinogenic substances.

7. Premalignant Oral Lesions.

These are usually of the leukoplakic variety and present evidence of "dyskeratosis" or dysplasia in addition to hyperkeratosis. In terms of therapy these lesions are to be regarded as early carcinomas and to be removed with adequate margins or destroyed with electrocautery or other procedures, (McCarthy and Shklar, 1964).

Bowen's disease of the mouth is an unusual variety of oral premalignant lesion. As previously mentioned, Bhaskar (1961) regards it as a variant of carcinoma in situ. Shafer, Hine and Levy (1963) describe it as a synonym for carcinoma in situ, and state that keratosis is not always present so that it may appear as an erythematous, velvety plaque, which may or may not be raised, and upon which whitish patches may be seen in some instances.

Pindborg et al (1963) describe a type of leukoplakic lesion which had characteristics of white patches on an erythematous background giving a "speckled" appearance, and which were often associated with "epithelial atypia" and carcinomas.

Gorlin (1950) described 6 cases of Bowen's disease, and seemed to feel that it was a laterally spreading intraepithelial type of superficial epithelioma.

The histologic features are usually described as being; hyperkeratosis (but not always), acanthosis, dyskeratosis, and variation in the size and shape of the epithelial cells of the spinous layer. Hyperchromatic nuclei are common, as are bizarre mitotic figures, and these frequently exhibit poikilocarynosis producing a multinucleated cell. The basal layer appears intact.

Bowen's disease is to be considered as an early malignant lesion and treated as such (McCarthy and Shklar, 1964). These authors also state that dyskeratotic changes are often seen in cases of papilloma and may signify the possibility of papilloma undergoing malignant transformation. They stress the importance of diagnosing and removing all papillomas of the oral mucosa.

8. Therapy.

Therapy of oral carcinoma at present involves surgery, radiation, or a combination of both. Radium needles and seeds implanted in tissue have value in certain cases. Chemotherapy has as yet proved of little benefit in the control of oral malignant disease, although it may offer hope for the future.

Espiner et al (1962), and Sullivan and McPeak (1962) have found the administration of methotrexate by intra-arterial infusion to be useful for palliation in advanced cases.

Kruger (1964) points out that planning of treatment depends on the histology of biopsy, location of the tumour and its radio-sensitivity, degree of metastasis, and the age and physical condition of the patient. 80% of cancers of the lip may be successfully treated by prompt therapy, but cancer of the floor of the mouth, tongue and

gingiva have a poorer prognosis. In the posterior part of the mouth, late discovery, rapid infiltration, and metastases cause a poorer prognosis than in the anterior region.

Surgery in a well-differentiated and reasonably small epidermoid carcinoma would involve local excision of the lesion with an adequate margin of normal tissue. The patient is kept under close observation, but prophylactic node dissection is not indicated. In a larger but well-differentiated oral carcinoma, the surgical approach is more radical, but, in the absence of palpable lymph nodes, prophylactic dissection is not indicated. Resection of bone is not indicated unless there is clinical or radiographic evidence of invasion into osseous tissue, (McCarthy and Shklar, 1964).

On the other hand, Southwick et al (1961) and Bucalossi and Ristro (1957) advocated that regional node dissection should accompany removal of the primary tumours of the tongue and floor of the mouth, as they found microscopic evidence of malignancy in 39% of lymph nodes which were clinically negative.

In a poorly differentiated or anaplastic carcinoma, the surgical approach must be radical, even in the absence of palpable nodes and obvious bone invasion.

The use of supervoltage radiation is becoming increasingly more popular and its advantages can be demonstrated. Cobalt 60 is now widely used in the therapy of oral carcinoma, and its "bone-sparing" action has been commented on. Meyer (1960) has shown, in experimental animals, that Cobalt 60 radiation applied to the jaws

produces considerably less damage to bone and soft tissue than an equal dose of 200 kv radiation. As techniques improve, super-voltage should permit the use of higher dosages of radiation without the serious problems of tissue damage and osteoradionecrosis.

9. Multiple Oral Malignant Lesions.

The concept of several oral malignancies occasionally arising simultaneously from separate foci was clearly stated by Slaughter in 1946 (quoted by McCarthy and Shklar, 1964) and appears to indicate that the entire oral mucosa in certain cases may have some predisposition to the development of neoplastic disease, either on a genetic or an environmental basis.

Cade and Lee (1957) state that multiple buccal tumours occur in 4.1% of cases.

Weisberger (1957) commented on the strong link between syphilis and leukoplakia, and that carcinoma is very likely when this combination exists. Further, there is a tendency for new carcinomas to form at locations which preclude the possibility of recurrence of the original malignancy.

Wilkins and Vogler (1957) presented a series of 81 cases of cancer of the gingiva, unusual in that 44 were females, and of these, 22 used snuff. 40% of the patients had leukoplakia on some part of the buccal mucosa in addition to cancer. In many patients it seemed that the cancer arose in an area of leukoplakia. Multiple primary cancers occurred in 14 (17%) concurrently or

following the gingival lesions. The frequency of leukoplakia in these patients was significantly higher than in those patients with one cancer. Of 67 with one cancer, 21 (31%) had leukoplakia, while of 14 with multiple carcinomas, 11 (79%) had leukoplakia. These data suggested that a patient with one cancer and leukoplakia has a greater chance of developing another primary lesion in the mouth than the patient with no leukoplakia. This observation led Wilkins and Vogler to believe that in many instances carcinoma of the mouth is the terminal manifestation of a chronically diseased mucosa.

Wynder and Bross (1957) found, in 543 patients with oral cancer, 59 had a history of multiple cancers. In 60% of these, the second or third cancer was in the upper alimentary or respiratory tract. Alcohol consumption and the history of syphilis were similar among patients with multiple primary cancers, but the percentage of excessive smokers among cases with double primaries was twice as high as in the remaining study cases. 19% of these cases had leukoplakia.

In Trieger et al's study (1959) of 68 patients with oral cancer, there were 12 additional primary carcinomas in 10 patients, occurring in the lung, oesophagus, tongue, larynx, uvulva, soft palate, and floor of the mouth.

Moertel and Foss (1958) aver that the idea that epithelial carcinoma originates from a single minute focus at a single instant in time has been challenged by the idea of multicentric origin of epithelial carcinoma. Of 732 patients at the Mayo Clinic with proved oral cancer from 1944 to 1953, 64 or 8.7%, had two or more discrete oral tumours. Of the 64, 21 occurred simultaneously, and

43 had lesions occurring at intervals varying from 1 - 25 years, the average interval being 7.1 years. Of these 64 patients, 48 (75%) had leukoplakia. The use of tobacco seemed to be an important factor. That the tendency to multicentricity in oral carcinoma is not limited to the oral cavity alone but extends to contiguous squamous cell mucous membrane is evidenced by the fact that an additional 55 of the 732 patients with oral cancer had associated epitheliomas of the lips, pharynx, larynx or oesophagus. Thus, the overall occurrence rate of multicentric carcinoma for the 732 patients is raised to 16.4%. When oral cancer develops, all of the contiguous squamous cell mucous membrane must be considered as highly susceptible to future malignant change. Frequent and regular follow-up examinations must be made so that any secondary lesions may be detected and treated early. Appropriate prophylactic measures should be initiated to eliminate any possible sources of carcinogenic irritation to these regions.

Lesney (1959) reported identical bilateral squamous cell carcinomas in an edentulous mouth on each end of the denture-bearing mucosa of the mandible. These were identical in the method of spreading as well as in position of occurrence.

Meyer and Shklar (1960) found 48 cases of multiple malignancy involving the oral mucosa and gastro-intestinal tract, out of a series of 768 cases. In 36 cases, there were multiple separate epidermoid carcinomas confined to the oral mucosa, while in 18 cases there were separate malignant tumours of the oral mucosa and other areas of the gastro-intestinal tract.

Cahn and Slaughter (1962) state that oral cancer seldom, if ever, arises from normal, healthy epithelium. There is usually a discernible pathological change that precedes irreversible neoplastic growth. Carcinoma originates not from a single cell that becomes malignant, but by a process of "field cancerization" wherein a whole area of epithelium undergoes neoplastic change at multiple points, with superficial and multiple foci coalescing to produce the single tumour. 11% of individuals with oral cancer develop a second separate cancer - an incidence far beyond the statistical occurrence of one oral cancer in the general public.

The findings of Sharp, Bullock and Hellsper (1963) were dealt with under Leukoplakia (Aetiology).

McCarthy and Shklar (1964) give the overall percentage occurrence of multiple carcinomas as 5. They report one case with 5 separate foci, and several cases with bilateral lesions. There was no evidence of metastasis to regional nodes in these cases, and the possibility of one lesion being a metastasis for the other was remote.

10. Spread of Oral Carcinoma.

Carcinoma of the oral mucosa will invade underlying tissue, but metastasis depends primarily upon the degree of malignancy. When oral carcinoma does metastasize, it spreads to regional lymph nodes. Topazian (1961) has pointed out that distant metastasis is more frequent than previously suspected, and in 83 autopsies, 24% (20 patients) had distant metastasis. The primary sites most frequently involved were the tonsils, floor of the mouth, palate and

tongue, and the lung was found to be the site of distant metastasis in 75% of the cases.

Well-differentiated oral carcinomas gradually invade underlying connective tissue and muscle. They eventually will penetrate into any bone that may underlie the site. Metastasis to lymph nodes will not occur, or will be a late development.

Poorly differentiated lesions will metastasize to regional lymph nodes early in their course of development.

The usual pattern of lymph node metastasis for carcinomas in the different areas of the mouth are as follows:-

<u>Primary site</u>	<u>Lymph node metastasis.</u>
Lower lip	Submental, submaxillary.
Upper lip	Submental, submaxillary.
Tongue	Submaxillary, jugular.
Buccal mucosa	Submaxillary.
Floor of mouth	Submaxillary, jugular.
Upper gingiva	Submaxillary, jugular.
Lower gingiva.	Submaxillary, submental, jugular.
Palate	Jugular.

Exfoliative Cytology.

Silverman et al (1958) expressed the opinion that exfoliative cytology offers an excellent adjunct to biopsy for the detection of cancer because of its simplicity and accuracy, and strongly urged it as a routine procedure for lesions of unknown aetiology when biopsy is delayed. It may prove valuable in suspected cases in which biopsy has failed to demonstrate a malignancy, and the two procedures can effectively be used simultaneously. Cytology can also be used in following treated oral malignancies to evaluate the effectiveness of therapy. Umiker et al (1960) and Sandler et al (1960) agreed, but emphasized that adequate biopsy is the diagnostic procedure of choice.

King (1963) asserted that cytodetection of oral neoplasms is accurate, causes no discomfort in the patient, and does not arouse his fear of cancer.

"The use of the smear technique (oral cytology) is of inestimable value to the dentist in general practice and to the dental specialists. It provides the dentist with a quick, painless, and uncomplicated method of examining a slightly suspicious lesion".
(Editorial, J.A.D.A., April, 1963.)

Cooke (1964) stated that exfoliative cytology usually plays a minor supportive role in a properly planned and carefully executed biopsy for diagnosing oral carcinoma. Definitive diagnosis is made by biopsy.

Sandler (1964) again emphasized that widespread application of this simple and painless technique should result in early disclosure of most mouth cancers.

Millard (1964), Williamson and Shapiro (1964), and McCarthy and Shklar (1964) all emphasized strongly that a smear is no substitute for biopsy, and that exfoliative cytology has a minor role to play in the detection of cancer.

This reviewer feels that present evidence substantiates the view of exfoliative cytology of the latter writers.

Papilloma.

Although many tumours or tumour-like lesions of the oral mucosa appear clinically as papillomatous lesions, the term papilloma is used specifically for a benign tumour of the epithelium. It is frequently confused with other benign intra-oral neoplasms, particularly fibroma.

Some authors, including Shafer, Hine and Levy (1963) state that a virus aetiology for papilloma is doubtful, as at present there has been no case of papilloma in the human being induced by injection of a cell-free extract of an oral papilloma from another person, although multiple oral papillomas do occur. Therefore they do not treat the subject "verruca vulgaris" separately. However, as other authors acknowledge verruca vulgaris in the mouth as an entity, a separate section will be devoted to it here.

A small separate section will also be devoted to inflammatory papillary hyperplasia and papillomatosis.

Papilloma will be discussed as follows:-

1. Clinical Features,
2. Aetiology,
3. Histologic Features,
4. Prognosis,
5. Treatment.

1. Clinical Features.

The usual appearance of papilloma is 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 and most commonly on the tongue, lips, buccal mucosa, gingiva and palate (particularly near the uvula).

Papillomas are usually only a few millimetres in diameter, but may grow up to several centimetres in size, (Shafer, Hine and Levy).

They may occur at any age, even in young children. Orlean (1956) reported the occurrence of two small papillomas on the tongue of a child three months old.

Thoma and Goldman (1960) distinguish between hard and soft papillomas. The soft papillomas are described as above, while the hard papillomas are said to occur in areas affected by advanced leukoplakia, and are produced by a localized progressive heaping up of keratinized epithelium. These authors also write of the fibropapilloma, which is a pedunculated fibroma with normal epithelial covering, although in some cases, elongation of rete pegs is conspicuous, but this is due to chronic inflammation rather than neoplasia.

McCarthy and Shklar (1964) state that in rare cases a papilloma may grow downward rather than outward, the clinical appearance being a slightly raised, nodular pink mass. The common exophytic type of papilloma is pink or occasionally white in colour, depending on the degree of keratinization. The base of the lesion may be a narrow pedicle or a relatively broad area. The neoplasm is firm to palpation, but rarely indurated at the base.

2. Aetiology.

Tiecke (1957) describes the papilloma as a benign epithelial tumour, and states that trauma, infection, metabolic disturbances and viral origin have been suggested as secondary aetiological factors.

Bernier (1959) writes that there is little specific knowledge of the aetiology. Sometimes the abundant overgrowth of the surface epithelium is a true neoplasia, stimulated by trauma, a primary infection, or a metabolic disturbance. More recently, some have suggested a virus origin, and this no doubt, is true in many instances.

3. Histological Features.

Various authors describe these as follows:-

Tiecke; The stratified squamous epithelium projects above the surrounding tissue in a tree-like fashion, supported by a connective tissue core, which is prominently vascularized. The epithelium is acanthotic, with a well-defined basal cell layer. Keratosis may be seen.

Bernier (1957); Referring to papilloma of the lip, Bernier stated that no dyskeratosis is seen, and little or no inflammation.

Bernier (1959); Hydropic degeneration may be noted, while keratotic activity varies markedly in advanced lesions and those subjected to trauma. Chronic inflammation may be present, and tends to be perivascular. Bernier describes a condition which he calls "Angiokeratoma", which shows acanthosis and keratosis, associated with a prominent vascular pattern.

Thoma and Goldman; In addition to the "soft" and "hard" papilloma, fibropapilloma is described, in which connective tissue plays the major role. The pedicle is wider, the epithelium shows proliferation, branching of the rete pegs, and a distinct germinative layer. There is often marked hyperkeratosis and acanthosis. Papillomas may show basilar hyperplasia, anaplasia and dyskeratosis, and in these cases, are precancerous.

Orban and Wentz (1960); The central fibrous tissue shows some fatty tissue, thin, narrow blood vessels, but no inflammation usually. The epithelium is thick and acanthotic. The clinical white appearance is due to the thickness of the epithelium, lack of blood vessels, and the wide parakeratotic layer.

Shafer, Hine and Levy; The essential feature is proliferation of spinous cells in a papillary pattern; the connective tissue forms the supporting stroma only, is not neoplastic. Chronic inflammatory cells may be present in the connective tissue.

Shira (1964); The hard and soft varieties differ only in the amount of keratinization present.

McCarthy and Shklar; The epithelium in papilloma invariably presents areas of dyskeratosis, with occasional large hyperchromatic nuclei and numerous mitotic figures. Differentiation microscopically from early carcinoma may often be difficult.

4. Prognosis.

Toto (1957) expressed the opinion that papilloma is generally benign, but may show acanthosis and rarely dyskeratosis with malignant

degeneration, while Halperin (1957) stated that it is safe to assume that lesions which appear clinically as papillomas must be considered as potentially malignant and managed accordingly. Gorlin (1957), on the other hand, stated that papilloma is always benign, and does not recur when removed; that he has never seen a premalignant growth. Those cases described as becoming malignant were probably confused with papillary, verrucous, or exophytic carcinoma. Bernier (1959) felt that the course of papilloma in the oral cavity is generally benign.

Thoma and Goldman quoted Ewing (1940) as stating that a gradual transformation of a benign papilloma into a malignant tumour has been fully demonstrated. However, the supposedly benign tumour, proved malignant after removal, may have been malignant from the beginning, while in other cases biopsy may have shown benignity, but serial section after removal showed carcinoma.. The transitional danger signals are fixation of the base and induration of the underlying tissues.

Thoma (1963) stated that malignant transformations occur frequently, but Shafer, Hine and Levy expressed the opinion that the possibility of malignant transformation is not great.

Shira averred that since papillomas protrude from the surface and are made up of proliferating epithelium, they are potentially dangerous. McCarthy and Shklar stated that the true papilloma is to be regarded as a benign neoplasm, with possible malignant potential. The degree of differentiation and the dyskeratosis may indicate histologically the possibility of early

malignant transformation. Biopsy of papillary lesions is absolutely mandatory.

5. Treatment.

All authors agree that the correct treatment of papilloma is excision. According to the individual author's view of the prognosis, as recorded above, so does his view vary as to the margin of tissue to be removed with the lesion.

Papillomatosis. (Papillary Hyperplasia).

1. Introduction,
2. Clinical Features,
3. Histologic Features,
4. Treatment and Prognosis.

1. Introduction.

The terms papillomatosis and papillary hyperplasia seem to be used interchangeably by many authors. This reviewer feels that papillomatosis used in its strict sense, would imply multiple true neoplastic papillomas, while the use of papillary hyperplasia would be confined to the inflammatory lesions of the hard palate commonly associated with denture-wearing. However, the conditions may be very difficult to differentiate, and, when this is the case, any distinction made would be only academic.

2. Clinical Features.

Thoma (1952) reported a case of papillomatosis, a grey lesion occupying the whole palate of a 56-year-old man who was edentulous, but had never worn a denture. Clinically the appearance was that of a squamous cell carcinoma.

Halperin (1957) describes the papillary hyperplasias as elevated, reddish, lobulated or papillary lesions, which are attached by a broad base, and which are associated with the relief chambers of dentures.

Thoma and Goldman (1960) state that, under the vacuum chamber of dentures, sometimes a large pedunculated papillomatous lesion results which is pressed into a recess formed in the mucosa

when the denture is worn, but when lifted away, the tumour is seen to be attached to the palatal membrane by a small pedicle. In other instances, the entire palate may be covered by diffuse multiple enlarged papillae, which, as Fisher and Rashid pointed out, can best be seen after washing away secretions and directing a stream of air upon the surface; this causes them to separate.

Shafer, Hine and Levy state that papillary hyperplasia may be considered an inflammatory condition associated in most instances with ill-fitting dentures and a poor state of oral hygiene. The condition appears rarely in patients with a full complement of teeth and no prosthesis. When an appliance is present, the site corresponds to the shape of the denture base, but sometimes only to the relief chamber. The lesion may occur in persons of any age or either sex. Each papilla is seldom more than 1-2 mms. in diameter. The tissue exhibits varying degrees of inflammation, but seldom is there ulceration.

Yrastorza (1963) found 64 instances of inflammatory papillary hyperplasia, discovered in examining 5,059 patients. These were found under "relieved" or "unrelieved" acrylic dentures, as well as under vulcanite dentures. In one patient a lesion was discovered in a palate not previously covered with a prosthesis. In this series, the lesion was believed to be irreversible, having persisted despite prolonged non-denture wear.

3. Histologic Features.

Thoma's case of papillomatosis was biopsied. One pathologist (Goldman) reported papilloma or papillomatosis, while another (Bernier)

reported leukoplakia, with dyskeratosis. Upon removal, serial sections revealed no malignant transformation.

Thoma and Goldman describe the histologic features of papillary hyperplasia as numerous papillary projections of hyperplastic epithelium which may be slightly keratinized. Hydropic degeneration is seen, the underlying connective tissue is loose and fibrous with a variable amount of oedema, while lymphocytes, plasma cells, and occasional leucocytes are present. Papillomatosis shows closely packed papillae, and keratosis in heavy smokers. The rete pegs are ramified, elongated, broadened by acanthosis, the basement membrane is intact; there is no invasiveness. Mitosis may be present, showing some bizarre figures. There may be dyskeratosis in the basal zone, where there is loss of polarity between cells, and hyperchromatic nuclei with vacuolization may be seen.

Other descriptions in the literature do not add anything to those quoted above.

4. Treatment and Prognosis.

The case of papillomatosis reported by Thoma in 1952 was quoted again by him in 1963, stating that the patient disregarding advice not to smoke, or chew tobacco, was seen 14 years after the original examination with a far-advanced carcinoma involving the entire palate and the maxillary sinus.

Sharp et al (1956) found that the mechanical trauma of negative pressure created by excessive relief of the palate of a

denture has a remarkably low relationship to carcinoma. The treatment is discontinuance of use of the denture. If inflammation does not subside promptly, a cautery-excision of the area is in order.

Halperin recommended leaving out the denture, then excising any unresolved part of the lesion, while Thoma and Goldman emphasized wide excision, followed by electrocoagulation or irradiation if the pathologic examination revealed malignancy.

Waite (1961) suggested leaving out the denture, then either removing the entire mucoperiosteum or using electrosurgery, while Bhaskar (1961) recommended correction of the ill-fitting denture accompanied by excision. Shafer, Hine and Levy stated that discontinuing the use of ill-fitting dentures and construction of new dentures, will generally result in regression of the oedema and inflammation, but the papillary hyperplasia persists. Yrastorza advocated suprapariosteal dissection.

Smith (1964) treated six patients with triamcinolone acetonide and found a remarkable improvement in 3 - 12 weeks. There was regression of inflammation, decrease in thickness, and a return to normal colour. The dentures were remade in each case.

Verruca Vulgaris (Wart).

McCarthy and Shklar state that warts or verruca are a specific viral infection of the skin and mucous membrane characterised by a local epithelial hyperplasia. They use the term moist warts or verruca acuminata for those that involve the oral mucous membrane, and use the following headings:-

1. Incidence,
2. Aetiology,
3. Clinical Manifestations,
4. Histopathology,
5. Diagnosis,
6. Therapy.

1. Incidence.

McCarthy and Shklar state that warts are becoming more common, and that the incidence of involvement of the oral mucous membrane is substantial. Children are most commonly affected, but occasional adult patients are observed. The warts in the mouth are usually the result of wart-laden fingers being placed there.

2. Aetiology.

Cuiffo and later, other observers, established the causative agent to be a filtrable virus that will pass Berkefeld filters of all grades of porosity, and induce warts in the skin of susceptible human beings.

It had been thought that one virus is responsible for all types of warts, but Lyell and Myles (in McCarthy and Shklar) conclude

that there are two types of warts caused by two different viruses. Bernier (1959) states that recurrence of verruca after removal lends support to the theory of their contagious nature. Bivins reported cultivation of the human wart virus in the chick chorio-allantoic membrane, but the experiment was not repeated, and Koch's postulants were not fulfilled. Mendelson and Kligman in 1959 reported success in culturing the wart virus on tissue culture composed of monkey kidney.

3. Clinical Manifestations.

Bernier (1957 & 1959) states that verruca occur most frequently on the labial mucosa, while McCarthy and Shklar report their occurrence also on all areas of the oral mucosa. The latter writers describe verruca as exuberant, nonhorny, and relatively soft, the colour usually being white, and the surface verrucous. There is no peripheral or deep induration since they are intraepithelial growths. Trauma is followed by brisk haemorrhage, due to their pronounced vascularity. They may be single, multiple, or they may coalesce. Rapid growth and development are the rule.

4. Histopathology.

The description of Bernier (1959) is as follows:-
The papillary character comes from elongation of the dermal papillae, but the main changes are in the epithelium. There is marked acanthosis with extensive hyperplasia of the stratum corneum, and marked keratosis either as parakeratosis, hyperkeratosis, or both. (McCarthy and Shklar state that the stratum corneum is composed almost entirely of parakeratotic cells). Bernier states that

there is little tendency for the rete pegs to go below the normal level of the basal layer, whereas McCarthy and Shklar find that the rete pegs may show such arborization that the picture of pseudo-epitheliomatous hyperplasia may result. Bernier continues that mitotic figures may be noted, and chronic inflammatory cells may occur in the corium close to the basal layer.

Bunting, Strauss and Banfield (1952) found that warts from which virus-like particles have been obtained are distinguishable by certain cytologic characteristics. There are eosinophilic intranuclear inclusion bodies and vacuolated cytoplasmic masses in the cells of these papillomas that are absent in the warts from which the particles have not been found, in spite of the papillomatous structure in both. Nuclear enlargement and distortion, the absence of mitotic figures, and interference in development of the epidermal cells probably all reflect the effect of the virus.

5. Diagnosis.

The rapid appearance and development, the verrucous surface, and the lack of depth and induration strongly suggest the true nature of the lesion. Associated skin lesions especially about the lips and fingers are corroborative evidence, (McCarthy and Shklar).

6. Therapy.

McCarthy and Shklar, and Bernier recommend excision for the simpler types, and the former state that light desiccation and curettage under local anaesthesia is successful, as is 20% podophyllin resin in alcohol application. Bernier recommends glacial acetic acid or trichloroacetic acid, radium or X-ray therapy also.

Lichen Planus

Lichen planus is a reasonably common inflammatory dermatosis involving the oral mucosa, and appears as localized white raised lesions with considerable variation in clinical appearance. Both the oral mucosa and skin are usually involved, but the oral lesions often occur in the absence of skin lesions. Lichen planus will be discussed under the following headings:-

1. Historical Review.
2. Occurrence.
3. Aetiology.
4. Clinical appearance of lesions and course;
 - (a) Cutaneous,
 - (b) Mucosal.
5. Symptoms.
6. Histopathology.
7. Diagnosis.
8. Differential diagnosis.
 - (a) Leukoplakia,
 - (b) Syphilis,
 - (c) Moniliasis,
 - (d) Aphthous ulcers,
 - (e) Mucous membrane pemphigoid,
 - (f) Pemphigus vulgaris,
 - (g) Chronic discoid lupus erythematosus,
 - (h) Erythema multiforme,
 - (i) Fordyce's spots.

9. Special topics;

Lichen sclerosis et atrophicus,

Lichen planus and pigmentation,

Lichen planus and psoriasis,

Lichen planus and oral malignancy,

Lichenoid stomatitis of Atabrine.

10. Therapy.

1. Historical Review.

This section has been adapted from the excellent historical review of McCarthy and Shklar (1964).

The disease was first described in 1869 by Erasmus Willson as leichen planus, "an eruption of pimples remarkable for their colour, their figure, their structure, their habits of isolated and aggregated development, their habitat, their local and chronic character, and for the melasmic stains which they leave behind them when they disappear". Among the numerous cases in his detailed study, eruptions are noted on the buccal mucosa, tongue and pharynx. The oral lesions in lichen planus were further noted and described by Unna and Crocker, the latter noting white lines and white spots on the buccal mucosa and symmetric plaques on the sides of the tongue in several cases.

Thibierge first described the oral lesions systematically. He felt that in most cases the lesions occurred on the buccal mucosa and the tongue, with certain differences in appearance. In the rest of the mouth, the papules were isolated or in small numbers.

Up to the time of Audry in 1894, it was felt that the oral

lesions were merely an accompaniment to the generalized skin eruption, but Audry pointed out that the oral lesions could occur alone. Poor first described the formation of "cavities" in lichen planus of the mucosa, corresponding in character to subepithelial bullae, and characterized by exudation from surrounding blood vessels.

Dubreuilh stated that the involvement of the oral mucous membrane alone was more common than involvement of the skin without mucosal lesions. He felt that biopsy studies showed the microscopic appearance of skin and oral mucosa were comparable in all points, and suggested biopsy for diagnosis. Lieberthal, who first described the oral manifestations of lichen planus in the American literature, realized that the lesions of the tongue differed from those of buccal mucosa. The tongue usually had irregular oval or circular plaques, while the cheek usually had papules, oval or circular plaques, most frequently, streaks or criss-crossing linear projections. Thus the pertinent facts concerning lichen planus had been set down with clarity by 1907.

2. Occurrence.

Unless otherwise acknowledged, material presented here will have been derived from McCarthy and Shklar (1964).

Trautmann, in addition to describing lichen planus bullosa, carried out a study of the medical literature up to 1910, and outlined a preliminary survey of the occurrence and disposition of the lesions of the oral mucosa in lichen planus. Oral lesions associated with skin lesions were observed in 94 of 157 cases of this dermatosis.

In 26 cases the lesions were confined to the oral mucosa. The location of the oral lesions was as follows; Cheek - 129 (82.10%); Tongue - 80 (50.09%); Lips - 35 (22.22%); Palate 27 (17.10%); Gums 17 (10.82%); while lesions of the larynx, vulva, tonsils, nasal passages and pharynx were considerably less frequent. Culver found oral involvement in 31 (23 buccal mucosa, 6 lingual) cases of 148 cases of lichen planus. Little reported mucous membrane lesions in 48 of 270 cases of lichen planus, and White found buccal mucosal lesions in only 15 and tongue lesions in only 2 out of 162 cases studied. Jacob found 17 cases with lesions in the mouth in 179 cases. Cawley and Kerr (1952) state that mucosal manifestations may precede, co-exist with, or follow skin lesions in 50% of cases. Cooke (1954) found that only 3 patients of his series of 50 with oral planus had accompanying skin lesions. Darling and Crabb (1954) quote Hellier as saying that lichen planus comprised 1.25% of all skin lesions treated, while Cheraskin and Langley (1956) stated that oral lesions are present in 50% of cases, being the only finding in 10%. Warin et al (1958) found that for every case presenting in the mouth, 5 or 6 cases of cutaneous lichen planus are seen. Orban and Wentz (1960) quoted a study giving the incidence as 21 of 58 patients, and that the lesions may be confined to the oral cavity in about 10% of the cases. Bhaskar (1961) gives the incidence as 50% of oral lesions, and states that the oral lesions may precede or follow skin lesions, or be limited to the oral cavity. Burket's figures are 1% of all skin diseases, and 50% occurrence of oral lesions compared to skin lesions.

Most authors seem to be agreed on the age incidence of lichen planus. It is commonly seen in the middle-aged individual, but numerous cases have been reported in children as well as in elderly individuals. The lesions of the oral mucosa can occur at any age. In Shklar and McCarthy's (1961) series, the ages ranged from 13 to 78 years.

McCarthy and Shklar (1964) state that lichen planus affects male and female in about equal numbers. Warin et al (1958) and Cooke (1954) found a female : male ratio of about 2 : 1, but other authors have reported a greater number of males affected.

McCarthy and Shklar give their opinion, based on clinical evaluation of a large series of patients, that most cases of lichen planus will eventually show lesions of both the skin and oral mucosa, irrespective of which appears first, if the patient is observed long enough and carefully enough. Likewise they feel that the classification of involvement in relation to different areas of the mouth is unreliable, although the buccal mucosa and tongue tend to be common sites of involvement, whereas gingival lesions are comparably rare.

3. Aetiology.

Cawley and Kerr, (1952); Nervous exhaustion or an emotional disturbance frequently antedates or coexists with lichen planus, but the cause remains an enigma. There is some evidence of a familial tendency.

Cooke (1954); In this series, the male patients all held positions of responsibility, or did precision work, while the females were housewives or people carrying more than usual responsibility.

The patients were sensitive, over-conscientious, and suffering from undue stress or anxiety.

Darling and Crabb (1954); The aetiology is unknown. The main theories are:-

1. Neurogenic; In a large number of cases, anxiety, worry, emotional shock are associated with the onset. Linear skin lesions may form in areas superficial to the area of nerve distribution.
2. Bacterial; Jacob and Helmbold, and Biberstein and Wachtel claim success using an antigen prepared from extracts of lesions, but do not implicate a specific infectious agent. There is no evidence for dental sepsis being involved.
3. Generalized toxæmia. Montgomery and Alderson suggest the origin of toxæmia as the alimentary canal.

There seems to be no evidence that the disease is in any way hereditary.

Cheraskin and Langley (1956) state that a definite familial relationship has been established.

Warin et al (1958); No relation to the wearing of dentures or smoking was found. Of 45 patients, 24 had histories of nervous breakdown, persistent insomnia, depression, 7 had had major worries immediately prior to the onset of the disease, and 4 had had previous peptic ulceration.

Bernier (1959); Not specifically known. It is believed to be associated with debilitating disorders such as shock, mental strain, etc.

Colby, Kerr and Robinson (1961); The aetiology is not known, but the disease is often associated with some degree of emotional tension.

Burket (1961); The exact cause is not known, but psychosomatic factors are considered important. Viral aetiology has been suggested, but not established. Burket, and others have observed that oral lesions of lichen planus develop in some patients with long-standing vitamin B complex deficiency.

Stones (1962); The aetiology is unknown. Psychosomatic factors may be important. Toxaemia may play a part, as the administration of certain drugs, such as arsenic, bismuth and gold (Gougerot) and quinacrine hydrochloride (Bazemore et al) may produce oral and skin lesions similar to those of lichen planus.

Shafer, Hine and Levy (1963); The cause is unknown. Mental strain seems to be important. Other causes which have been suggested include traumatism, malnutrition and infection; hereditary causes have been suggested, but unsubstantiated.

McCarthy and Shklar (1964); The cause is not well understood, though psychosomatic as well as hereditary factors appear to play an important role. A summary of other theories is; (1) traumatic, (2) specific bacterial, (3) syphilitic, (4) parasitic, (5) viral, (6) mycotic, (7) allergic, (8) toxic, (9) nervous or neurogenic, (10) hereditary, (11) psychosomatic. These authors' impression based on a large series of cases is that lichen planus represents a reaction of the skin and mucous membrane to some form of emotional trauma. They noticed that frequently the particular incident may have reached

a conclusion before the first symptoms of lichen planus occur, and feel that the frequent association is more than coincidence.

Further evidence to support this concept is the absence of lichen planus among the psychotic. Psychiatric evaluation of patients with lichen planus may reveal significant information.

As the opinions of so many experienced clinicians and pathologists on the aetiology of lichen planus are so nebulous, any comment by this reviewer could only be wildly speculative and useless.

4. Clinical Appearance of Lesions.

(a) Cutaneous Lesions.

Cawley and Kerr (1952); The basic lesion is a round or annular flat-topped papule, covered with a fine scale, possibly umbilicated, 1-3 mms. in diameter. There are fine white lines on the papules called Wickham's striae. The papules may remain discrete or coalesce, and are firstly bright red, then reddish-purple. When the eruption clears, hyperpigmented macules persist for weeks or months. The main sites are the flexor aspects of the wrists and lower legs, while the scalp, forehead, face, palms and soles are rarely involved.

All other authorities read give practically identical descriptions of the cutaneous lesions of lichen planus to Cawley and Kerr.

(b) Mucosal Lesions.

Cawley and Kerr (1952); The characteristic features are porcelain-white dots, and streaks arranged in a criss-cross fashion, producing a reticulated pattern. Round or annular lesions occur on the tongue, while erosions and ulcerations occur at times, especially on the buccal mucosa.

Cooke (1954); The types of pattern seen are:-

1. Linear - the commonest pattern seen on the cheeks.
2. Discrete papular - usually on the cheeks and tongue.
3. Confluent papular. This type is often observed, giving white raised patches simulating leukoplakia and often covering a great part of the cheek. This pattern occurred less often on the tongue, giving the appearance of tiny pieces of cotton-wool resting between the papillae. In cases of long-standing, it was associated with the loss of the filiform papillae, giving it a smooth, glazed appearance.
4. The reticular pattern, often on the cheek, has a characteristic lace lattice-work appearance, but on the tongue it is seen imposed on a smooth glazed appearance with a complete absence of papillae. This was also the pattern most commonly found on the gingivae.
5. The annular pattern. Papules are arranged in circles up to 1 cm. in diameter enclosing an erythematous mucosa. This pattern was seen alone or in combination with the discrete papules on the cheek and palate.
6. Pigmented pattern - brown papules and plaques were seen on posterior aspects of both cheeks. White keratinized areas occurred in the centre of the brown patches and independently of them.
7. Vesicular or Bullous - one case only occurred in the series, together with a typical reticular pattern. A blister about 1" X $1\frac{1}{2}$ " formed about twice a month, burst, and left a shallow ulcer which healed in a day or two. The diagnosis was confirmed by biopsy.

8. Atrophic or erosive form - these occurred on cheeks and tongue. The epithelium is dry, shiny, atrophic, with bright red erythematous areas up to 1 cm. in diameter, often with discrete white lines at the margin.

Darling and Crabb (1954); The lesions are the same as on the skin, varying only in the site and structure of the lesions, but moisture and trauma modify the appearance of lesions in the mouth and in cases with associated ulceration, secondary infection may further distort the clinical picture. The lesions are less easily recognized and harder to diagnose, than those on the skin.

The initial mouth lesion is a white papule, the size of a pinhead, conical or flattened in shape, and the surrounding mucous membrane may be normal, or show varying degrees of inflammation. The papules are soft to touch, ulceration is considered rare, but may be more frequent than hitherto reported. Where the bullous form occurs, vesicles may be seen on occasion in the early stages, but these rapidly break down in the mouth, becoming ulcerated and sore.

Papules coalesce to form plaques, but papules are usually found at the margins. The most characteristic form is a lace-like network with thickened nodules at the intersections of striations comprising the network. Papules may aggregate, or by a circular grouping, present the annular form. These forms are commonly seen on the buccal mucosa, particularly level with the plane of occlusion.

Where there is a considerable increase in keratinization of the mucous membrane, a verrucous lesion occurs which may be difficult to distinguish from early leukoplakia.

On the lips, the papular nature of the lesion is seldom seen, except on the inner mucosal surface, and crusting and erosion may occur, obscuring the true nature of the lesion, but in such a case close examination may reveal small areas of a fine white network or isolated papules with radiating striae. In severe cases cheilitis may occur and a purulent discharge follow.

Lesions have been described on all accessible mucous membranes of the body, and show comparable appearances to those of the oral cavity.

After involution, the oral lesions do not usually present residual pigmentation.

Darling and Crabb describe a rare acute form, the greater part of the body being covered with lesions in 24 to 48 hours. In the chronic or more common form, the disease develops gradually, and constitutional symptoms rarely occur. Some patients may show only isolated lesions, and where the oral lesions precede or follow those of the skin, the interval may be months or even years.

On involution, evidence of lesions may remain as temporarily pigmented spots on the skin, and in many patients, the disease eventually dies down of its own accord in months or years, though recurrence is likely even after apparently successful treatment. There are variable periods of recurrence and remission.

Darling and Crabb (1955) presented three cases with associated ulceration, pointing out the likelihood of misdiagnosis, as the striations and papules may be overlooked. In one case, a condition lasting five years, there were varying periods of remission,

and recurrences lasting a few days to three months. The other two were unusual in that there was ulceration which persisted without healing, in one case for more than a year, in the other case ten years.

Warin et al (1958); The clinical appearance was as described by Darling and Grabb. One patient complained of blisters, but these were not seen. There was ulceration in 30 patients out of 45, on the cheeks in 19, tongue in 8 (sides 4, dorsum 3, ventral 1). The ulcers were superficial, with a red granular base, sometimes with a slough at the base. The condition cleared up in only 4 cases, but was still present after one year in 2 patients, after 5-10 years in 5, after 3-5 years in 7, 1-3 years in 15, less than one year in 8.

The descriptions of McCarthy and McCarthy (1958), Bernier (1959), Orban and Wentz (1960), and Thoma and Goldman (1960) do not differ in any important respect from earlier ones.

Warin (1961) points out that over half the cases of lichen planus develop superficial ulcerations, often recurring on the same site, and often associated with local trauma from dentures and teeth.

Bhaskar (1961) and Golby, Kerr and Robinson (1961) present mainly similar descriptions to the foregoing.

Burket (1961); The lesions are grouped into (1) non-erosive and (2) bullous forms;

(1) Non-erosive form; These are raised, bluish-white, diffusely outlined, hyperkeratinized areas, with a linear, reticular or a confluent papular arrangement. Small raised areas may be present

where linear hyperkeratinized lesions intersect.

The cheek lesions may be bilateral, diffuse, there is no loss of elasticity, while characteristic radially arranged dendritic projections may be seen at the periphery.

Similar lesions may be present on the tongue, palate, and vermilion border of the lower lip. Lateral tongue lesions are usually linear in type, but on the dorsum, geometrically shaped plaques. Dorsal lesions do not affect flexibility or cause papillary atrophy. (Note that Cooke, 1954, states that papillary atrophy does occur). Lingual lesions are usually an accentuated purplish colour.

The vermilion border of the lower lip may be obscured by the fine network of bluish-white or purplish lines, these lesions being seen most clearly when moistened and stretched.

(2) The bullous or erosive form; The protective epithelial covering becomes separated from the underlying tissues, leaving raw, eroded, painful lesions. The lesions may appear from the beginning as multiple eroded areas, or may simulate a herpetic vesicle, and then present erosions varying from a few mms. to several cms. in size. Radially arranged white dendritic extensions can usually be seen at the periphery.

Bullous lesions may involve the cheek mucosa, the edentulous alveolar tissues, gingiva and palate, but are infrequent on the tongue. Periods of spontaneous remission and exacerbation occur, the latter possibly coinciding with some emotional upset or the menstrual period in the female.

Shafer, Hine and Levy (1963); These authors describe the classical pattern of radiating white or grey, velvety, thread-like lines criss-crossing in a reticular pattern most commonly seen bilaterally on the buccal mucosa. At the intersection of the striae of Wickham, a tiny, white elevated dot is present. Plaques may form with striae radiating from the periphery.

Vesicle and bulla formation is not a common finding. This form usually begins as such, and not as a progressive lesion of the non-erosive type. Striae may usually be seen at the borders. A hypertrophic form may occur, generally appearing as a well-circumscribed, elevated white lesion resembling focal keratosis.

Oral manifestations commonly occur weeks or months before skin lesions; most patients with oral lichen planus do not have skin lesions at the time of presentation. Many never manifest the cutaneous form, but most patients are not followed up for long enough to be certain of this.

Other mucous membranes may be affected also, such as the penis, vagina and epiglottis.

McCarthy and Shklar (1964); The fundamental lesion is a small papule, pinhead in size, domed, and glistening white ("mother-of-pearl white). The papules may be somewhat flattened, and may be grey. On the tongue, the papules tend to be more flattened and do not glisten.

The appearance of the lesions depends on the arrangements of the papules into lines, circles, plaques, and other shapes.

Buccal mucosa - About 85% of cases present involvement of the buccal mucosa. The following patterns are described; reticular; punctuate; linear; plaque; papular; erosive or ulcerative (very few seen on the buccal mucosa, usually at the line of occlusion, related to trauma); vesicular (rare).

Tongue - The following patterns occur; reticular, annular (the centre of the rings undergoes atrophic changes, becoming red and smooth); verrucous (uncommon, only within areas of extensive involvement); erosive or ulcerative (usually with lines at the borders); atrophic (an atrophic glossitis develops very similar to that of tertiary syphilis, leading to confusion in the early literature; the tongue usually is red, oedematous, this form tending to occur in elderly females); bullous or vesicular pattern (rare, but more common on the tongue, usually on borders or ventral surface, variable in size, white or grey-purple in colour, the entire epithelium lifts, secondary infection may occur, striae are usually present at the margins); plaque pattern (grey-white, not raised, as they replace atrophied lingual papillae, may even appear sunken, are fairly dense, patchy in distribution).

Lips - lichen planus is seldom on the lips; if it appears, it is usually on the lower lip, nearly always accompanied by buccal lesion. The patterns usually seen are reticulated, striated and annular. Rarely, ulcerative or vesicular lesions may appear. These lesions may simulate forms of cheilitis, and make diagnosis difficult if no typical lesions are present.

Floor of the mouth - Lesions do occur rarely. The authors report a case of reticular lesions in a 13 year old girl.

Gingiva - The lesions, usually reticulated, occur on the attached gingiva, sometimes extend on to the marginal gingiva. Desquamative lesions sometimes occur. The authors feel that desquamative gingivitis is a nonspecific gingival manifestation of a variety of systemic disturbances, and it is not surprising to find it associated with lichen planus.

5. Symptoms.

There is general agreement in the literature on the symptoms of lichen planus. These are usually absent in oral lesions, although with skin lesions there tends to be a severe pruritis. In the oral cavity there may be mild subjective symptoms, usually described as a "burning" or "irritation". In rare cases, a "burning tongue" may signify lichen planus rather than the usual papillitis and glossitis.

The lesions are usually discovered accidentally when the patient feels them with his tongue, or sees them in a mirror, or when they are noticed by the dentist or physician.

If the lesions are erosive or bullous in nature, symptoms may be severe. Some patients experience extreme pain from the eroded areas and are as uncomfortable as those suffering from bullous eruptions such as pemphigus or erythema multiforme.

6. Histopathology.

Goldman et al (1951); There is a varying degree of hyperkeratosis, irregular acanthosis, liquefaction degeneration of the basal layer, and a bandlike infiltrate in the lamina propria. In

some instances, the rete pegs were completely absent, while in others they were of irregular length with a tendency for pointing of the lower end - the "saw-tooth" configuration. In some instances, the basal layer could hardly be discerned. The infiltrate, of lymphocytes and histiocytes, tended to border the epithelium, but at times extended more deeply. Some inflammatory cells were seen in the epithelium.

Cawley and Kerr (1952); The cutaneous lesions show hyperkeratosis, accentuation of the granular layer, irregular acanthosis, dissolution of the basal layer, a band-like infiltration in the upper third of the dermis. The dissolution of the basal layer may lead to vesicle formation. Hyperkeratosis and accentuation of the granular layer do not occur consistently on the mucous membranes.

Cooke (1954); The cardinal changes in the mucous membrane of the cheek appear to be:-

- (a) Hyperkeratosis, and an increase in the granular layer out of proportion to the degree of keratinization, or a para-keratosis.
- (b) Acanthosis, and in some cases, a saw-tooth appearance to the epithelial ridges.
- (c) A liquefaction degeneration in the basal cells.
- (d) Subepithelial oedema which, if extensive, separates the epithelium from the corium.
- (e) A lymphocytic infiltration limited to the upper and middle layers of the dermis, and having a well-defined lower margin. Plasma cells are only rarely present.

- (f) In the atrophic form, a hyper- or parakeratosis and atrophy of all the layers of the dermis is associated with the above changes. These histologic changes vary in degree from case to case, and sometimes the sub-epithelial oedema is very slight indeed.

Darling and Crabb (1954) give the sequence of changes in the skin as follows; increased vascularity of papillary and sub-papillary regions of the corium; a dense cellular infiltrate in these regions; increase in size in the stratum granulosum, with acanthosis and hyperkeratosis; oedema may occur between the basal layer and the infiltrate, but not usually so; the outline of the basal layer becomes indistinct, the cells being separated by the infiltrate; the rete pegs become shortened, absent or have a saw-tooth appearance, possibly due to pressure from the infiltrate; the cell boundaries of the Malpighian layer become lost and the nuclei indistinct or missing, so that groups of cells seem fused and present a homogeneous appearance.

The infiltrate is mainly lymphocytes, but polymorphs may also be present and may be seen in the early lesion grouped around the dilated vessels. In some cases chromatophores loaded with pigment are found in the dermal papillae of the skin lesions, and the pigment has been described as melanin.

In the obtuse and verrucous forms, the epidermis is greatly thickened, producing the dome-shaped nodule and warty outgrowth respectively. In the bullous lesion, the oedema becomes sufficient to lift the epidermis completely off the dermis, giving rise to a

vesicle, thus modifying the usual clinical picture. The atrophic lesion seems to represent an involutionary type in which the epidermis is greatly thinned, the underlying dermis being sclerotic, so that clinically the lesion appears as a white spot. The histopathology of the rare erythematous lesion has not been described, but it would seem that the redness might be ascribed an enhancement of the increased vascularity of the simple lesion.

In the mouth, hyperkeratosis, the increase in the granular layer are not so marked, melanin has not been reported.

The discussion by Cooke, and Darling and Crabb, was so comprehensive and thorough, that attention will only be drawn to any divergence or changed emphasis in the writings of other authors.

Orban and Wentz (1960) do not mention the "saw-tooth" configuration of the rete pegs, but emphasize the focal infiltration of the subepithelial connective tissue by lymphocytes and the absence of plasma cells as being important diagnostic features.

Shklar and Meyer (1961) state that the typical "saw-tooth" configuration seen in skin lesions is usually absent from mucosal lesions - in many instances the rete pegs are flattened.

Cahn et al (1961) comment that with haematoxylin and eosin staining, the basal membrane is vague, washed out, invaded by the sub-epithelial inflammatory infiltrate. It appears there is no basement membrane. Sections stained with paS disclose a basement membrane that clearly stands out.

Shafer, Hine and Levy (1963); The histological features are characteristic and pathognomonic. They draw attention to the

appearance of a thin band of eodinophilic coagulum in the place of the basal layer. True dyskeratosis does not occur. An artefactual tearing is often seen between the connective tissue and epithelium, suggesting a weakness between these two structures. Although obviously a post-surgical technical flaw, it is sometimes of aid in establishing the diagnosis.

McCarthy and Shklar (1964); Pa-S staining for mucopolysaccharides shows a well-outlined basement membrane area which is sharply defined, but relatively thin. The inflammatory zone beneath the epithelium is well stained, as are the blood vessel walls and connective tissue. There is often an intense reaction in the stratum germinativum. Fibrillar extensions are noted running from the basement membrane area into the underlying inflammatory zone. The epithelial cells are relatively free of mucopolysaccharides, but the zone of parakeratosis often stains deeply.

7. Diagnosis.

McCarthy and Shklar (1964) state that a diagnosis of lichen planus cannot be made in terms of histopathology alone. There must be a correlation with clinical evidence, including the appearance and distribution of the lesions and the course of the disease. In biopsy reports they prefer a description of the lesions in microscopic terms and a diagnosis of "chronic inflammation consistent with a diagnosis of lichen planus". In the absence of clinical manifestations, it is doubtful that one could diagnose lichen planus, though the suspicion of its presence may be reasonably strong. A negative microscopic report does not rule out the possibility of lichen planus. Indeed,

many cases with classic clinical manifestations present a classic microscopic picture only late in the course of the disease or not at all. Chronicity is the rule, and a course of several months to a year is typical.

Not all authors share these views. Cawley and Kerr state that the microscopic features are typical, while Cooke states that diagnosis is easily made clinically in the typical form, but in the erosive form, biopsy is necessary, and apparently conclusive. In this regard, most other authors feel that the biopsy specimen must include some striated area to be conclusive in the case of the erosive or vesicular types. Darling and Crabb (1955) comment that ulceration associated with lichen planus does not have distinctive features, and is likely to be misdiagnosed, as the striations and other clinical features may be overlooked. Bernier (1959) states that the microscopic features are characteristic, but not as characteristic as in the skin lesions, while Shklar and Meyer (1961) point out that diagnosis depends on correlation of clinical and microscopic evidence. Burket (1961) feels that in the case of the non-erosive form, the clinical features lead to the diagnosis, while in the bullous form, search for and biopsy of the hyperkeratotic lesions may be helpful. Shafer, Hine and Levy state that the clinical characteristics are usually sufficient for diagnosis, but biopsy may be necessary, and the microscopic features are characteristic and pathognomonic, while striae may usually be found at the periphery of the bullous lesions. Biopsy is necessary for diagnosis of the hypertrophic lesions.