

ORAL PRECANCEROUS LESIONS

Hetessy¹²⁵ states that there is considerable controversy about the use of the term 'precancerous', based on the experience that there can be no certainty that a benign oral lesion will undergo malignant degeneration, the possibility of such an occurrence being estimated as from one to ten per cent. On the other hand, Cahn⁴⁷ believes that oral cancer seldom, if ever, arises de novo from normal health epithelium, but there is usually a discernible pathological change that precedes irreversible neoplastic growth.

Hertz,¹¹² defines precanceroses as changes in the tissues which may assume malignant characteristics at anytime, and yet remain unchanged for a considerable period, particularly if irritations are avoided. On the other hand, Weisberger³⁹⁰ states that when a sufficient number of oral carcinomas arise at the site of an existing non-malignant lesion, it is assumed that this lesion has the potentiality of developing cancer, and it is frequently spoken of as a precancerous lesion.

Hahn, Morgenoth and Themann³⁷¹ indicate that the concept of a precancerous change of the oral mucosa is based upon clinical experience that certain changes in the protective epithelium are more or less certain to lead to malignancy. Lederer and Skolnik¹⁶⁴

state that pathologically, precancerous lesions are conditions which, in inherently cancer-susceptible individuals, have a tendency to undergo malignant transformation when subjected to chronic irritation over a long period. They emphasize that this does not mean that cancer is always preceded by a precancerous lesion, or that every precancerous condition will inevitably lead to cancer. Sharp and Spickerman³⁴⁶ stress that precancerous lesions are not the "cause" of cancer, the term merely connotes the existence of certain abnormal conditions under which malignancy is likely to occur, or under which such a course will occur in a fair percentage of cases.

Against the concept of a precancerous state, Lederer and Skolnik¹⁶⁴ point out that many small cancers cannot be demonstrated to follow those preliminary changes that are supposed to be associated in the change from premalignant to malignant condition. They indicate that thus, carcinomas of the oral cavity associated with papilloma are believed by many to be independent of one another, except that the papilloma may be a result of the already existing irritation that also was a factor in cancer development, or the subsequent irritation by the cancer.

All this serves to emphasize the importance of exercising caution when evaluating the potential

malignant degeneration of a precancerous lesion, or when assessing whether a carcinomatous lesion has evolved from a premalignant condition.

LEUKOPLAKIA

The term 'leukoplakia' is derived from the Greek word 'leucos' which means white, and 'plakos' meaning tablet or block. The term was coined by Schwinner of Budapest in 1877.^{339, 369}

A review of the literature shows the confusion in the usage of this terminology. To some,^{51, 170, 306, 339, 391, 398} leukoplakia is a clinical term for a white patch or plaque on the mucosa, carrying no specific histologic connotation. Used in this sense, it generally embraces a number of different white lesions of varying origin, and is therefore solely descriptive of the macroscopic appearance of the lesion and is in no way diagnostic. However, traditionally the term leukoplakia carries the implication of a potentially dangerous or perhaps premalignant lesion. This introduces an element of dissatisfaction because, although some of the white lesions are potentially dangerous and may proceed to malignant degeneration, the vast majority of them are innocuous, non-malignant lesions of the oral mucosa.

As pointed out by Lucas,¹⁷⁰ in recent years, many investigators suggest that the designation of

leukoplakia should be reserved for lesions that reveal histological changes considered to indicate premalignancy. To this end, certain definite criteria such as cellular atypia and dyskeratosis are being established. Sprague³³⁹ points out the two most common sets of criteria that have been used. The first requires the presence of acanthosis, hyperkeratosis, and an inflammatory infiltrate in the superficial lamina propria. This is a rather old concept and has almost been completely superseded by the current one, which requires the presence of malignant dyskeratosis and atypia of the epithelium. Shklar³⁰³ indicates that the term dyskeratosis is an unfortunate choice, because it appears to describe an abnormality in the epithelial maturation rather than a basic cellular abnormality suggestive of anaplasia. He feels that a term such as epithelial dysplasia is more meaningful. Used in connection with such histologic connotations, leukoplakia implies a potentially dangerous lesion capable of malignant transformation.

This confusion in terminology has some real clinical and histopathological significance and, for this reason, some authorities such as Kollar et al.,¹⁵⁷ Donaldson,⁷⁹ and Smillie³¹⁴ suggest that the use of the term leukoplakia should be discontinued altogether. As a substitute, Kollar and his colleagues¹⁵⁷ present

a simple classification for maturation disorders of the mucous membranes as follows:

1. Hyperplasia
2. Hyperkeratosis
3. Hyperkeratosis and inflammation
4. Hyperkeratosis, dyskeratosis, and inflammation
5. Intraepithelia cancer
6. Epidermoid cancer

They indicate that the advantages of their classification are:

- (i) the microscopic meaning of leukoplakis is eliminated
- (ii) a discussion as to whether it is benign, cancerous or precancerous can be avoided
- (iii) a basis for a rational plan of management is provided, and this is most important.

On the other hand, Chromet et al.⁵² suggest re-defining leukoplakia as the "histologic triad of hyperplasia, hyperkeratosis or parakeratosis, and inflammation," and that proliferative and neoplastic changes of the oral epithelium be classified as follows:

1. Hyperplasia
2. Leukoplakia
3. Dysplasia
4. Carcinoma-in-situ
5. Early invasive carcinoma
6. Carcinoma

Bernier¹⁶ emphasizes the now popular concept that dyskeratosis must be present if the lesion is to be judged as potentially malignant and called leukoplakia. He and Tiecke³⁶⁰ differentiate this from the innocuous lesion without the characteristic of dyskeratosis, which they termed pachyderma oris.

Smillie³¹⁴ distinguishes between a benign dyskeratosis and a malignant dyskeratosis, the former includes changes associated with conditions that are known to be non-neoplastic, while the latter includes features such as an increased and, particularly, abnormal mitoses, disorientation of cells in the deeper layers, variations in nuclear staining, variations in cell and nuclear size and shape, and hyperplasia of basal cells. He adds that the changes of malignant dyskeratosis represent a step in the production of a frank carcinoma.

Hahn, Morgenroth and Themann,³⁷¹ after an exhaustive investigation of 152 cases of leukoplakia using clinical examination, stomatoscopy, vital staining with Schiller's iodine solution, cytologic examination, light microscopy, electron microscopy, and biochemical examination categorise leukoplakia into the following groups:

GROUP I Leukoplakia caused by simple epithelial hyperkeratosis

GROUP II Leukoplakia caused by more severe superficial parakeratosis, or genuine superficial keratinization

GROUP III Leukoplakia caused by a combination of hyperplasia and keratosis

GROUP IV Leukoplakia with atypical epithelial behaviour.

Shklar³⁰³ claims that clinically, there are several types of leukoplakia, and they may be classified according to their extent and severity of involvement of the oral mucosa as follows:

1. Diffuse initial involvement
2. Diffuse moderate involvement
3. Diffuse severe involvement
4. Localised initial involvement
5. Localised moderate involvement
6. Localised severe involvement.

LEUKOPLAKIA AND ORAL CANCER

There is unanimous agreement by many authorities 47, 106, 112, 127, 164, 227, 250, 251, 260, 277, 280, 303, 318, 319 that leukoplakia is a precancerous lesion, and that malignancy does follow in a proportion of cases. What is controversial here is the percentage of cases that undergo malignant degeneration, both with regard to the incidence of co-existing leukoplakia in patients with carcinoma, and to the incidence of leukoplakic lesions that subsequently become carcinomatous.

I. COEXISTING LEUKOPLAKIA WITH CARCINOMA: So far as co-existing leukoplakia and carcinoma are concerned, the

figures given by various authors vary considerably. Lucas,¹⁷⁰ after an extensive review of the literature, states that the reported figures range from some 2 per cent. to 75 per cent.

Wynder, Feldman and Bross,³⁹⁴ in a study of 543 patients with oral malignancy, report that 19 per cent. had leukoplakia. This corresponds to the findings of Silverman et al.³²⁷ who indicate that 19 per cent. of 834 patients with oral cancer investigated by them had leukoplakia.

In a large review of 14,162 Indian patients with cancer of the mouth, Paymaster²⁴² reports that 30 per cent. had leukoplakia, and this corresponds to the findings of McGrath and Schimdt¹⁸² in their series of 117 patients.

Sharp and Hazlet,³²² in a survey of 100 patients with oral carcinoma, noted that the association between leukoplakia and primary carcinoma was about 60 per cent. in the lingual, buccal, gingival, and palatal regions, and about 80 per cent. in the floor of the mouth, while Weisberger³⁹⁰ reports a 60 per cent. coexistence of leukoplakia and oral cancer in 275 patients.

The findings of Archer and Morris⁹ was that 15.8 per cent. of 203 patients with oral malignancy had leukoplakia, while Meyer and Shklar¹⁸⁵ report that 26 per cent. of a series of patients with multiple oral

cancers had leukoplakia.

The coexistence of leukoplakia and malignancy of specific intraoral sites are as follows (Table 10).

II. INCIDENCE OF MALIGNANT DEGENERATION IN LEUKOPLAKIA:

When the proportion of leukoplakic lesions that can reasonably be interpreted as proceeding to malignant degeneration and, subsequently, giving rise to cancer is considered, again there is wide variation in the findings of different investigators. Shafer and Waldron³¹⁹ indicate that in the older literature this was estimated to be about 30 per cent., but in their series, and that of Cooke⁵⁷ and Renstrup,²⁸⁰ the incidence of such malignant transformation in leukoplakia was much lower.

Hahn, Morgenroth and Themann³⁷¹ are of the opinion that malignant degeneration occurs in 10 per cent. of all patients with leukoplakia, and that this figure rises to 34.5 per cent. in patients with Group IV type of leukoplakia as presented in their classification. On the other hand, Lederer and Skolnik¹⁶⁴ claim that malignant degeneration occurs in 30 per cent., and that 50 per cent. of lingual cancer develop from pre-existing leukoplakia.

In an analysis of hospital records of 1,272 patients with oral cancer, Hobaek¹²⁷ reports that in 16 per cent. of cases the carcinomatous lesions developed from pre-existing leukoplakia. This

TABLE 10 •

COEXISTING LEUKOPLAKIA WITH CANCER

Site of cancer	Author	No. of Patients with the cancer	Percentage of Leukoplakia
LIP	WARD and HENDRICK ⁴⁰¹	259	17
LIP	CROSS, GURALNICK and DALAND ⁶⁵	563	14.5
LIP	SMITH ³³¹	129	11
LIP	SCHREINER and CHRISTY ³⁰²	636	2.4
TONGUE	ARIEL ³	---	10 to 40
TONGUE	RAHAUSEN and SAYAGO ²⁸¹	113	11
TONGUE	TRIEGER et al. ³⁶⁵	108	14.8
TONGUE	PAYMASTER and SHROFF ²⁴⁴	700	32
FLOOR OF THE MOUTH	MARTIN and SUGARBAKER ¹⁹⁷	103	25.
FLOOR OF THE MOUTH	GARDNER, BOWEN and BROWN ¹⁰⁶	28	3.5
BUCCAL MUCOSA(CHEEK)	MARTIN and PFLUEGER ²⁰⁰	99	22
BUCCAL MUCOSA(CHEEK)	PAYMASTER ²⁴¹	650	20
BUCCAL MUCOSA(CHEEK)	JACKSON and NEW ¹⁴²	107	15
BUCCAL MUCOSA(CHEEK)	O'BRIEN and CATLIN ²³⁸	248	18
BUCCAL MUCOSA(CHEEK)	JORSTAD ¹⁴⁴	70	10
PALATE	MARTIN ¹⁹⁹	74	27
GINGIVA	WILKINS and VOGLER ⁴⁰⁶	81	40

corresponds closely to the findings of Pindborg,²⁵⁰ who, in a review of 35 patients with the speckled-type of leukoplakia, reports that 14 per cent. revealed carcinomatous changes as shown by biopsy. From a review of the literature, he²⁵¹ presents the following table in an attempt to assess the rate of malignant transformation in these lesions (Table 11).

He indicates that unfortunately most authors have not defined the term leukoplakia in their investigations, and hence the uniformity of the clinical materials reviewed is questioned.

Sarnat and Schour³⁰¹ mention a case reported in which an initial diagnosis of leukoplakia of the tongue was made from biopsy, and eighteen months later, biopsy of the same lesion indicated carcinoma. They are of the opinion that in most cases the leukoplakia probably does not develop into cancer. This opinion is shared by Strickland³⁴¹ who estimates that probably only one per cent. of all patients with leukoplakia will develop carcinoma arising from the leukoplakic area. He reports that in a small group of patients with leukoplakia which he has kept under observation for eight years or more, none had undergone malignant degeneration. Sharp, Bullock and Hazlet³²³ indicate that taking a time factor as a guide to assess the potentiality of malignant degeneration is not reliable,

TABLE 11

RATE OF MALIGNANT TRANSFORMATION IN ORAL LEUKOPLAKIAS
OBSERVED OVER AN EXTENDED PERIOD OF TIME

Author	Country	Year	No. of Patients Observed	Rate of Malignant Trans- formation %	Observ- ation Period years
SKACH, SVOBODA and KUBAT	Poland	1960	71	1.4	3-6
SUGAR and BANOCZY	Hungary	1959	86	6	11
STURGIS and LUND	United States	1934	298	12	5
LEONARDELLI and TALAMAZZI	Italy	1950	268	20	1 month - 15 years
WEISBERGER	United States	1957	22	36	4

Source: PINDBORG²⁵¹

because some patients with leukoplakia have been followed for from five to twenty-five years without any sign of malignant degeneration in the lesion, while in others, cancer of the tongue has been seen to develop within six to eight weeks.

Weisberger³⁹⁰ observed 22 patients with microscopic diagnosis of leukoplakia closely for four years, and at the end of this time, eight developed a carcinoma in the leukoplakic site. He is of the opinion that if syphilis is present together with leukoplakia, there will almost be a 100 per cent. malignant degeneration. This is based on his observation that in 14 patients in whom leukoplakia and syphilis were present, all developed cancer at the sites of these lesions.

Bhaskar²⁸ estimates that 25 per cent. of patients with leukoplakia will develop a malignancy at the sites where the leukoplakic lesions are present. Pindborg²⁵⁰ indicates that most of the figures given in the literature regarding malignant transformation refer generally to selected groups of individuals in whom the leukoplakia was seen co-existing with carcinomas, and there is no valid assumption to interpret them as undergoing malignant transformation into frank carcinomas. All this serves to emphasize the current consensus of opinion that it is almost impossible to determine the incidence of malignant transformation in the majority of cases.

GENERAL INCIDENCE

Most authorities agree that leukoplakia occurs fairly commonly in the oral cavity, especially in persons over the age of forty, although reliable statistics of its incidence in population groups are difficult to obtain.

Castigliano⁵¹ claims that the incidence of leukoplakia in the general population is about 1 in 500. On the other hand, Kephart (quoted by Bernier¹⁶) states that the incidence is 1 in 50 in persons past the fourth decade of life.

Bruszt (quoted by Pindborg²⁵¹) reports that 3.6 per cent. of 5,613 individuals examined in the rural districts of Hungary had leukoplakia. This corresponds closely to the findings of Shafer and Waldron,³¹⁹ who, in an analysis of 8,554 biopsy specimens of lesions from the oral cavity, indicate that four per cent. of the lesions were leukoplakia.

Pindborg²⁵¹ investigated the occurrence of this condition in various Indian dental colleges, and tabulated his findings as follows (Table 12):

Besides occurring in the oral cavity, leukoplakia is also found on the mucosal surfaces of the upper respiratory tract, vulva, uterine cervix, urinary bladder, and renal pelvis.^{51, 106, 318}

TABLE 12

FREQUENCY OF ORAL LEUKOPLAKIA IN DIFFERENT LOCALITIES,
INDIA

Locality	No of patients examined	Percentage with leuko- plakia
LUCKNOW (Uttar Pradesh)	10,000	3.3
BOMBAY (Maharashtra)	10,000	2.8
BANGALORE (Mysore)	5,612	1.6
TRIVANDRUM (Kerāla)	2,000	1.1

Source: PINDBORG²⁵¹

SEX INCIDENCE

The consensus of opinion is that leukoplakia of the oral cavity is more prevalent among men than in women^{106, 170, 390, 395, 398} Bernier¹⁶ and Knutson¹⁵⁰ estimate that the male to female ratio is 95:5 in favour of men.

The findings of various investigators on the sex distribution of this condition are contained in the following table (Table 13).

Castigliano⁵¹ indicates that the incidence in men has dropped from 95 per cent to 65 per cent in the last two decades.

AGE INCIDENCE

Many authorities^{150, 164, 395, 398} indicate that oral leukoplakia is seen more commonly in persons of older age group. Castigliano,⁵¹ Lucas,¹⁷⁰

TABLE 13
SEX DISTRIBUTION OF ORAL LEUKOPLAKIA

Author	Year of Report	Percentage	
		Men	Women
HOBÆK ¹²⁷	1946	73.6	26.4
RENSTRUP ²⁸⁰	1958	66.0	34.0
LEDERER and SKOLNIK ¹⁶⁴	1959	76	24
SHAFFER and WALDRON ³¹⁹	1961	68	32
PINDBORG ²⁵⁰	1963	59	41

Bernier,¹⁶ and Weisberger³⁹⁰ share the opinion that this condition is seen predominantly in the fourth and fifth decades of life.

Waldron and Shafer,³¹⁹ in an analysis of 332 patients with oral leukoplakia, report that 80 per cent. of them were over the age of 40 years. This closely parallels the findings of Renstrup,²⁸⁰ who, in a smaller review of 90 cases, reports that 90 per cent. of the patients were over 40 years old.

Hobaek,¹²⁷ in an investigation of 246 cases, indicates that the average age of the patients was 60.1 years, with the greatest number in between the ages of 50 and 70 years. However, he adds that in the series, persons of about 30 years of age with this condition were by no means rare.

The age and sex distribution of oral leuko-

plakia according to Shafer, Hine and Levy³¹⁸ are as shown in the following diagram (Figure 3).

SITE OF OCCURRENCE

Although leukoplakia may occur anywhere in the oral mucosal surface, observations made by different investigators seem to indicate a predilection for certain intraoral sites. The findings of various investigators for the site distribution of this condition in the oral cavity are summarised as follows:

RENSTRUP²⁸⁰ - buccal mucosa and commissures, alveolar mucosa, tongue, lip, hard and soft palate, floor of the mouth, and gingivae.

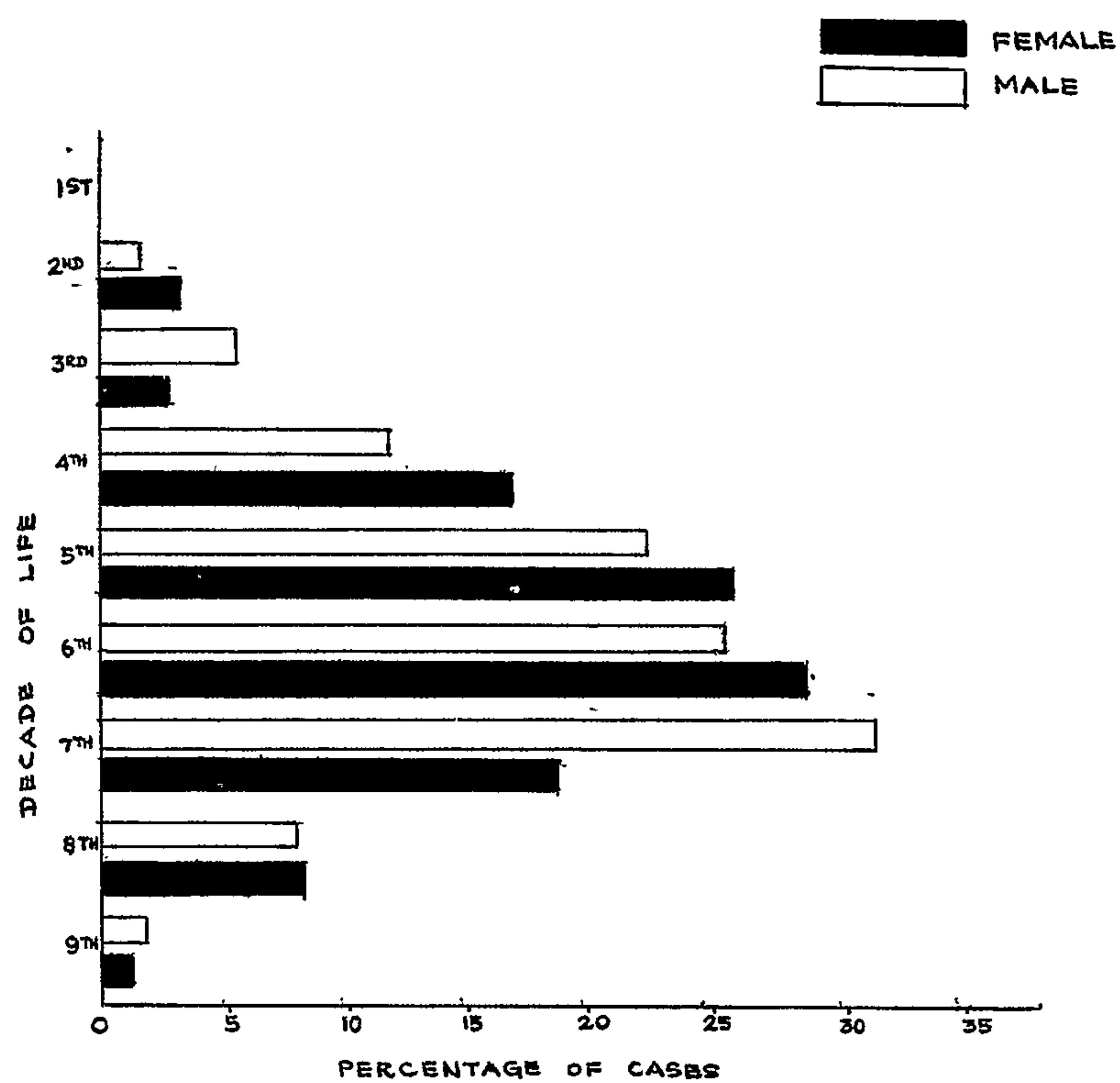
SHARP, BULLOCK and HAZLET³²³ - tongue, buccal mucosa, gingivae, hard palate, and lips.

HOBÆK¹²⁷ - tongue and floor of the mouth, lower lip, buccal mucosa, palate and gingivae.

SHAFFER and WALDRON³¹⁹ - mandibular alveolar ridge, gingiva or muco-buccal fold; buccal mucosa, palate, maxillary ridge, gingiva and muco-buccal fold, floor of the mouth, lower lip, retromolar area, and tongue.

CASTIGLIANO⁵¹ - cheek (near commissures and along the occlusal line), tongue, floor of the mouth, palate, undersurfaces of tongue and edentulous ridges.

Figure 3



OCCURRENCE OF LEUKOPLAKIA BY AGE AND SEX
(321 cases: Male 219, Female 102)

Source: SHAFER, HINE and LEVY³¹⁸

Pindborg,²⁶⁰ in a study of oral leukoplakia in India and in Denmark, present the following table comparing the site distribution of patients with this condition in the two countries (Table 14)

TABLE 14

LOCALIZATION OF ORAL LEUKOPLAKIAS IN LUCKNOW,
INDIA, AND COPENHAGEN, DENMARK

Localization	LUCKNOW	COPENHAGEN
	328 patients with 510 leukoplakias	211 patients with 373 leukoplakias
	%	%
Labial commissure	48.0	13.1
Buccal Mucosa	40.1	42.9
Lips	4.6	10.2
Alveolar Ridge	3.3	13.1
Tongue	2.7	7.7
Gingiva	0.9	1.9
Palate	0.4	7.4
Floor of Mouth	-	3.7
TOTAL	100.0	100.0

Source: PINDBORG²⁶⁰

As can be seen from the table, the most striking differences are the more frequent involvement of the labial commissure in Indian patients, and no leukoplakias were located on the floor of the mouth in these people. Pindborg²⁶⁰ states that the frequent involvements of the labial commissures were due to bidi-smoking.

ETIOLOGY

Numerous etiologic and predisposing factors are cited as responsible for oral leukoplakia. Most investigators,^{16, 51, 112, 127, 164, 280, 318, 390, 395, 398} in a discussion of the etiology of this condition, list a multitude of factors which can be broadly grouped under two main categories, namely, extrinsic local factors, and intrinsic predisposing or systemic factors. Factors which have been indicted as offenders include tobacco, alcohol, syphilis, vitamin deficiencies, hormonal disturbances, galvanism from dissimilar metallic restorations and local irritations from sharp, malposed or carious teeth, ill-fitting dental appliances, oral sepsis, and poor dental restorations.

The use of tobacco has been evaluated by many investigators^{16, 51, 112, 127, 164, 260, 318, 319, 398} as of considerable etiologic significance. Many of the chemical constituents of tobacco and its combustion end products such as tar, which contains phenolic bodies and ammonia compounds, are irritating to the oral mucosa and capable of producing leukoplakic changes. Weisberger³⁹⁰ is of the opinion that pipe smoking is most harmful, with cigarette smoking at the other end of the scale and tobacco chewing in between.

Trauma, or local chronic irritation, from cheek biting, ill-fitting dentures, sharp, broken down teeth, faulty restorations, oral sepsis, and the liberal use of caustics are considered by some authorities^{16, 51, 280, 318} to be extremely important in the etiology of this condition.

The use of alcohol, especially undiluted alcohol, has also been implicated as of etiologic significance in oral leukoplakia.^{112, 164, 395, 398} On the other hand, Shafer, Hine and Levy³¹⁸ indicate that people who are heavy smokers are usually also inveterate drinkers, and this makes it difficult to establish the role of alcohol in the development of this condition.

Although syphilis has been rated as of fairly importance in the etiology of oral leukoplakia, especially syphilitic glossitis, the findings of Hobaek,¹²⁷ Cooke,⁵⁷ and Renstrup²⁸⁰ seem to discount such a relationship. They are of the opinion that the role of syphilis in this regard is of minor significance.

Nutritional deficiencies, especially those from vitamin A and vitamin B complex, have been suggested as important predisposing factors in oral leukoplakia by some investigators.^{51, 164, 232, 318, 398} This is based mainly on the findings that vitamin A deficiency will induce metaplasia and keratinization of certain epithelial surfaces. Shafer, Hine and

Levy³¹⁸ indicate that the mechanism for this is unknown, but it might be related to the alteration in oxidation patterns of the epithelium, making it more susceptible to irritation. MacComb¹⁷⁸ states that the poor nutritional status as seen in most alcoholics may predispose to leukoplakia.

Evidence relating to an association between leukoplakia and hormonal disturbance is mainly of an indirect nature. Thus Weisberger,³⁹⁰ in treating 65 women patients who had leukoplakia with estrogenic hormones, reports that the results obtained were encouraging. Shafer, Hine and Levy³¹⁸ draw attention to the lack of investigation in this field, which makes it difficult to evaluate its etiologic significance.

Hertz¹¹² regards galvanism as of importance in the etiology of leukoplakia. However, in recent years, there is a tendency to discount such a relationship.^{16,318}

Most of the factors enumerated so far seem to be capable of promoting oral leukoplakia, mainly through chronic irritation to the mucosal surface. However, Cooke⁵⁷ points out that leukoplakia is also seen in the mouths of non-luetic patients, non-smokers, teetotallers, as well as in patients who are edentulous, or in those whose mouths are dentally fit. He is of the opinion that factors such as smoking and irritation influence the prevalence or degree of this condition, but are not

always responsible for it. He indicates that such local factors tend to precipitate the development of leukoplakia in the mouths of susceptible patients where the constitutional tendency exists. This opinion is shared by Weisberger,³⁹⁰ and Sharp, Bullock and Hazlet.³²³

Swan,³⁴³ in an extensive review of the literature, summaries the opinions of 36 authors regarding the significance of the various etiological factors as follows:

LOCAL FACTORS:

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

PREDISPOSING FACTORS:

- 18 authors found nutritional factors significant
- 16 authors found syphilis significant

8 authors found hormonal factors significant

5 authors found heredity significant

CLINICAL FEATURES

Clinically, the appearance of leukoplakia varies considerably.

Hobaek¹²⁷ distinguishes two principal forms of leukoplakia - 'leukoplana' which is a smooth, non-ulcerated type, and 'leukoverrucosa' which is thicker and has a verrucous appearance. He claims that all leukoplakia begins as the non-ulcerated type and most lesions eventually end up in the verrucous form.

Shafer, Hine and Levy³¹⁸ indicate that leukoplakia vary from a non-palpable, faintly translucent white area, to a thick, fissured, papillomatous, indurated lesion. The surface of the lesion is frequently finely wrinkled or shrivelled in appearance, and may feel rough on palpation. The colour is white, grey, or yellowish-white, but if tobacco stain is present, it may assume a brownish-yellow colour.

Bernier¹⁶ states that the size of the lesion varies greatly, and the colour may vary from white to grey, and at times pinkish when little or no keratin is present, while Bhaskar²⁸ describes the lesions clinically as a white, flat or raised, rough or smooth patches of varying sizes, which sometimes present ulceration.

Chromet, Niebel and Valaitis⁵² differentiate three types of small lesions of the order of approximately 5 mm. in diameter:

- 1) simple leukoplakias which are white to greyish-white patches, presenting no hyperaemic margins, and which can be rubbed off.
- 2) suspicious lesions which are cuddled plaques with peripheral hyperaemia, and can be rubbed off, but will recur fairly soon.
- 3) the probable early carcinomatous lesion which exhibits scuffing of the mucosa, peripheral hyperaemia and superficial ulceration.

Lederer and Skolnik¹⁶⁴ broadly divide leukoplakia into three forms, namely, the smooth variety, the raised (plaque) type, and the verrucous or papillomatous form, while Pindborg²⁵⁰ describes a 'speckled' type which appears as a white patch, either in a nodular or a more diffuse form, interspersed with erythematous areas.

According to Sharp, Bullock and Hazlet,³²³ leukoplakic lesions may be opaque, thick or thin, white, hornified, leathery plaques, exhibiting various degree of irregularity and roughness of the surface.

Renstrup²⁸⁰ points out that chronic leukoplakia may be diffuse or ill-defined, slightly elevated and of varying extent in size. The lesion is frequently

whitish, greyish, or yellowish-white in colour. In early lesions, a smooth or slightly rough, leathery and wrinkled surface is quite characteristic, and occasionally a completely pearly, smooth appearance is seen. In advanced lesions, ulcerations, fissuring or verrucous formations are quite common.

HISTOPATHOLOGY

Shafer, Hine and Levy³¹⁸ indicate that most authorities, regardless of their criteria for a microscopic diagnosis of this condition agree that leukoplakia represents a dysplasia of the epithelial surface.

A review of the literature shows that a wide range of histologic terminology has been used to give a microscopic description of this lesion. These include keratosis, leukokeratosis, hyperkeratosis, hyperkeratosis complex, hyperkeratosis simplex, non-specific keratosis, focal keratosis, pachyderma oris, acanthosis, epithelial hyperplasia, and parakeratosis. All these terms inevitably would lead to confusion, since there is diverse interpretations of them by different authorities. In recent years, numerous investigators^{16, 28, 323, 337} include the pre-requisite of dyskeratosis for a microscopic diagnosis of leukoplakia and, in this sense, the term leukoplakia connotes a precancerous lesion capable of undergoing malignant degeneration.

The presence of inflammatory cell infiltration

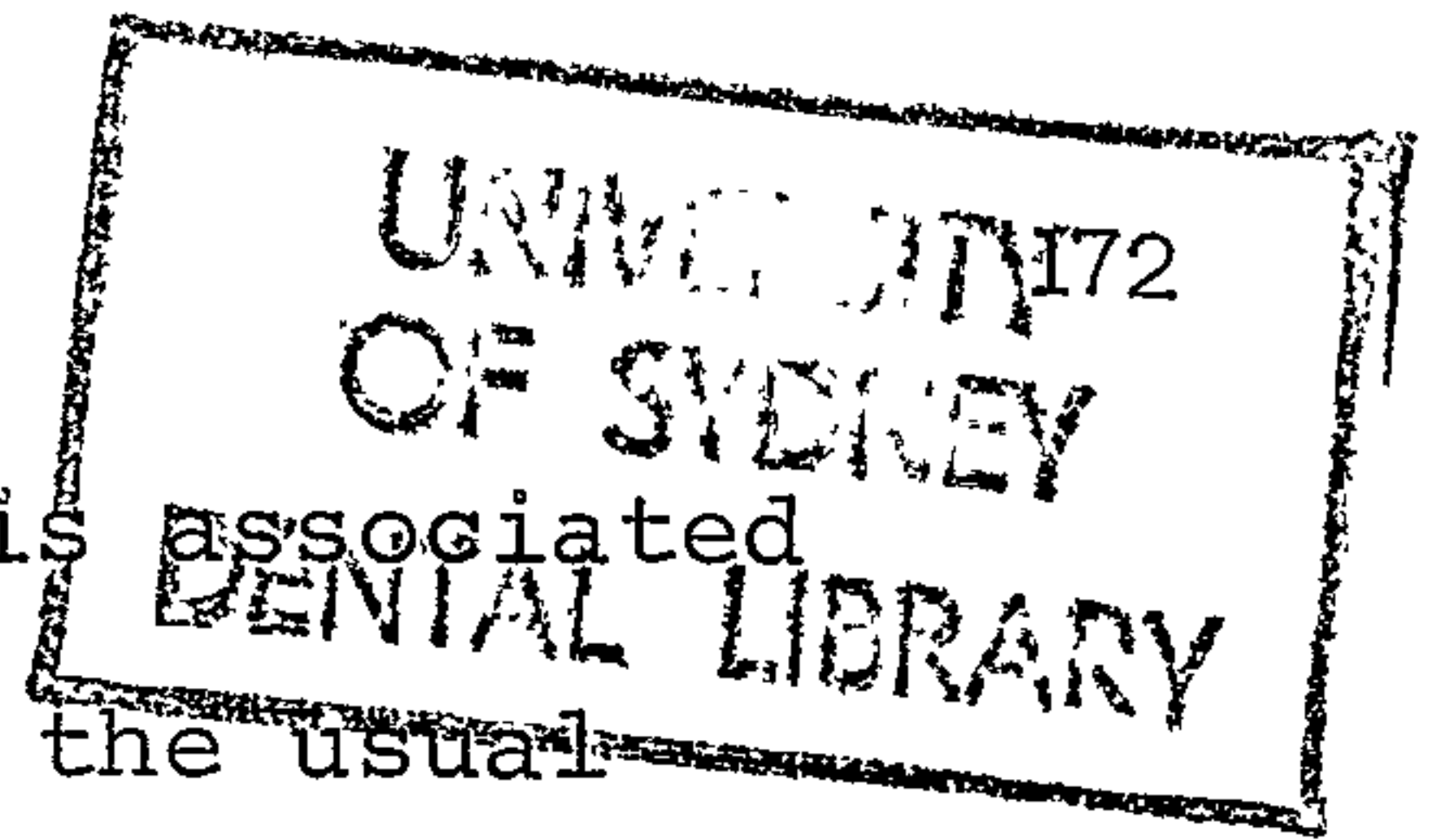
in the underlying connective tissue has been discussed by these investigators, although the significance of this finding is not clearly understood. The inflammatory reaction may not be related to the lesion per se, but rather, it is a response of the tissue to irritation produced by the various factors operating to give rise to leukoplakia.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of leukoplakia from other white lesions of the oral cavity is essential before treatment of the condition is instituted. White lesions of the oral mucosa to be differentiated from leukoplakia include lichen planus, syphilis, psoriasis, lupus erythematosus, mycotic infections (chiefly moniliasis) white spongy nevus, chemical burns, pemphigus, erythema multiforme, herpes simplex, and early epidermoid carcinoma.

Although a differential diagnosis from such an exhaustive list is not easy, a careful and systematic approach is important, utilizing case history, clinical examination, pertinent laboratory tests, and biopsy.

From a clinical point of view, lichen planus is probably the most important lesion to consider in the differential diagnosis of oral leukoplakia.^{51, 318} Castigliano⁵¹ suggests the use of Lugol's solution as a clinical diagnostic test for leukoplakia. He



indicates that the area of hyperkeratosis associated with clinical leukoplakia will not take the usual deep mahogany stain because of the decrease in glycogen content of the cells in such lesions.

Perhaps the most reliable means of establishing a definitive diagnosis in most white oral lesions is by biopsy.

TREATMENT

The treatment of oral leukoplakia varies considerably, depending mainly on its microscopic diagnosis. It includes such modalities as surgical excision, electrocautery, X-ray therapy, fulguration, the removal of local irritating factors, and the administration of vitamin A, vitamin B complex, and estrogens.

Hobaek¹²⁷ suggests the removal of irritations from tobacco, sharp teeth, dentures, and the improvement of oral hygiene. He indicates that radium may be used for cases exhibiting gross histological atypia, and electrocoagulation in uncomplicated cases.

Shira³⁵⁷ advises complete removal of those lesions exhibiting dyskeratosis, and in lesions that do not lend themselves to surgical procedures, dessication or electrocoagulation may be used.

MacComb¹⁷⁸ advocates conservative treatment first, such as removal of any irritating factors

(e.g. cessation of the use of alcohol, tobacco, etc.), improvement of oral hygiene, and the maintenance of a well-balanced diet, before attempting any definitive treatment of the lesion itself by complete surgical excision or electrocautery. He stresses that radiation therapy in any form is contraindicated.

Lederer and Skolnik¹⁶⁴ also advocate conservative treatment as the first approach before any radical procedure is made in the form of X-ray therapy, electrocautery, surgical diathermy, and any chemical means of eradicating the lesion. They lay emphasis on treatment of systemic conditions and the correction of any vitamin deficiency.

Bernier¹⁶ and Bhaskar²⁸ are of the opinion that where dyskeratosis is seen, surgery, electrodessication, or endothermy are indicated to effect complete removal. They feel that the elimination of local irritants and the administration of hormones and drugs alone will not suffice in these cases.

Waldron³⁹⁸ indicates that in lesions which exhibit significant cellular atypia, excision, stripping or fulgeration is the treatment of choice, whereas in lesions showing only benign epithelial hyperplasia, a more conservative approach is indicated, such as the elimination of tobacco, alcohol, and other local irritating factors, the institution of good oral hygiene,

and the administration of vitamin A and vitamin B.

Shafer, Hine and Levy³¹⁸ state that basically, the treatment of oral leukoplakia is aimed at the elimination of any recognizable local irritating factors. They advocate total excision or cautery for small lesions, and multiple-stage stripping, with or without skin grafting, for extensive lesions. They discourage the use of X-ray irradiation.

Sharp³²¹ treated a selected group of patients with precancerous oral lesions using a special regimen which involved the systematic regulation of the diet with hydrochloric acid supplements, and nutritive additives in tablet form containing dessicated liver, vitamin B₁₂, riboflavin and folic acid. He reports that superficial leukoplakia frequently regresses and disappears when patients are maintained on such a regimen, and that even the more advanced plaque-like type of leukoplakia show signs of regression.

It appears that the consensus of opinion in the treatment of this condition is a conservative approach first before any radical procedure is attempted, depending on the histologic findings.

PLUMMER VINSON SYNDROME

This condition was first described by Plummer in 1914, and later in 1922 Vinson supplemented his observations.^{51, 321, 390} It is also sometimes

termed Kelly-Patterson syndrome because of studies made by them in 1919.⁸

There is unanimous agreement by several investigators^{3, 51, 164, 170, 248, 318, 380, 393} that this syndrome is a precancerosis. Ahlbom⁸ was one of the first to show a definite correlation between this condition and cancer, particularly malignancy of the hypopharynx, oral cavity, and oesophagus. In his investigation of 150 women with squamous cell carcinomas of the oral cavity, pharynx, and oesophagus, who attended the Radiumhemmet in Stockholm for treatment, he found that 70 per cent. of them had positive signs and symptoms suggestive of Plummer Vinson syndrome.

Weisberger³⁹⁰ observed eighteen women patients suffering from this condition over a period of from four to eight years and noted that all of them had carcinomas, either at their first visit or developed it under observation. He indicates that in many instances there was a tendency of recurrence following treatment of the original carcinomas, and that one patient has had seven new carcinomas so far. However, in two patients who discontinued the use of dentures after treatment of the original carcinomas, there was no recurrence of the malignancy following an eight year observation period.

Plummer Vinson syndrome is predominantly a disease of Swedish women, especially those living in rural areas of the northern parts of Sweden.^{3, 8, 112, 248, 318} Wynder et al.³⁹³ observed that for male patients, a definite association was found only for those with cancer of the lower hypopharynx, while in women it is significantly associated with malignancy of the oral cavity, hypopharynx, and oesophagus.

Shafer, Hine and Levy³¹⁸ indicate that women suffering from this syndrome are usually in their fourth and fifth decades of life, while Ahlbom⁸ gives a wider age range of from 15 to 50 years.

Patients suffering from Plummer Vinson syndrome present various clinical signs and symptoms.^{8, 16, 51, 164, 318, 380, 390, 393} These include dysphagia, long-standing hypochromic microcytic anaemia, cracks or fissures at the corner of the mouth, dry and narrow (fish-type) mouth, thin lips, early loss of teeth, smooth, red, painful tongue with atrophy of the filiform and fungiform papillae, alchorhydria, general atrophy of the mucous membranes of the mouth, pharynx, and oesophagus, exhibiting a loss of normal keratinization, koilonychia (spoon shaped finger nails), brittle nails, moderate enlargement of the spleen, a lemon tinted pallor of the skin, listlessness, ankle edema and dyspnea, excessive menstrual bleeding, and

occasional kraurosis.

Ahlbom,⁸ Uthman,³⁸⁰ and Shafer, Hine and Levy,³¹⁸ state that the anaemia associated with this syndrome is due to an iron deficiency, which may arise through:

1. chronic blood loss as in patients with a history of profuse menstruation,
2. an inadequate iron supply in the diet, or
3. a faulty iron absorption mechanism, which is generally caused by alchorhydria since the absence of hydrochloric acid prevents the conversion of unabsorbable dietary ferric iron to the absorbable ferrous iron.

That the anemia is of an iron deficiency type can be confirmed by the lack of a reticulocyte response following the administration of vitamin B₁₂. Shafer, Hine and Levy³¹⁸ further suggest that the atrophic changes seen in the mucous membranes of the alimentary tract, which predisposes to the development of carcinomas in these sites, may be caused directly by the depletion of iron stores in the body, since the integrity of the epithelium is dependent upon adequate serum iron levels.

Wynder et al.³⁹³ indicates that the dysphagia itself, if not due to web formation, may frequently be due to the atrophic changes of the musculature of the oesphagus which may lead to stricture. So far as

their precancerous nature is concerned, the changes in the epithelium include hyperkeratinization and an increase in the mitotic activity of the basal layer. Weisberger³⁹⁰ reports that metabolic studies of excised mucosa from patients with this condition is suggestive of an abnormal pattern of oxidative mechanism of such tissues before the development of carcinoma.

Some investigators^{8, 164, 393} share the opinion that one of the important causes of this condition and, thus ultimately, one of the promoters of cancer is dietary abnormality. Ahlbom⁸ reports that in Sweden, the poorer section of the population exists on a diet which is undoubtedly deficient in iron, and this possibly could be related to the numerous cases of carcinoma in women seen in his studies. Wynder et al.³⁹³ noted that the outstanding feature of the diet of the population group with this syndrome is an almost total lack in fresh meat, fresh-water fish, green vegetables, and fresh fruits. On the other hand, the diet consists substantially of potatoes, butter, milk, cheese, gruel, porridge, and salted herrings. This type of diet is low in vitamins, particularly vitamin C, and rich in carbohydrates. They postulate that the deficiency of vitamin C, which led to an almost endemic sub-

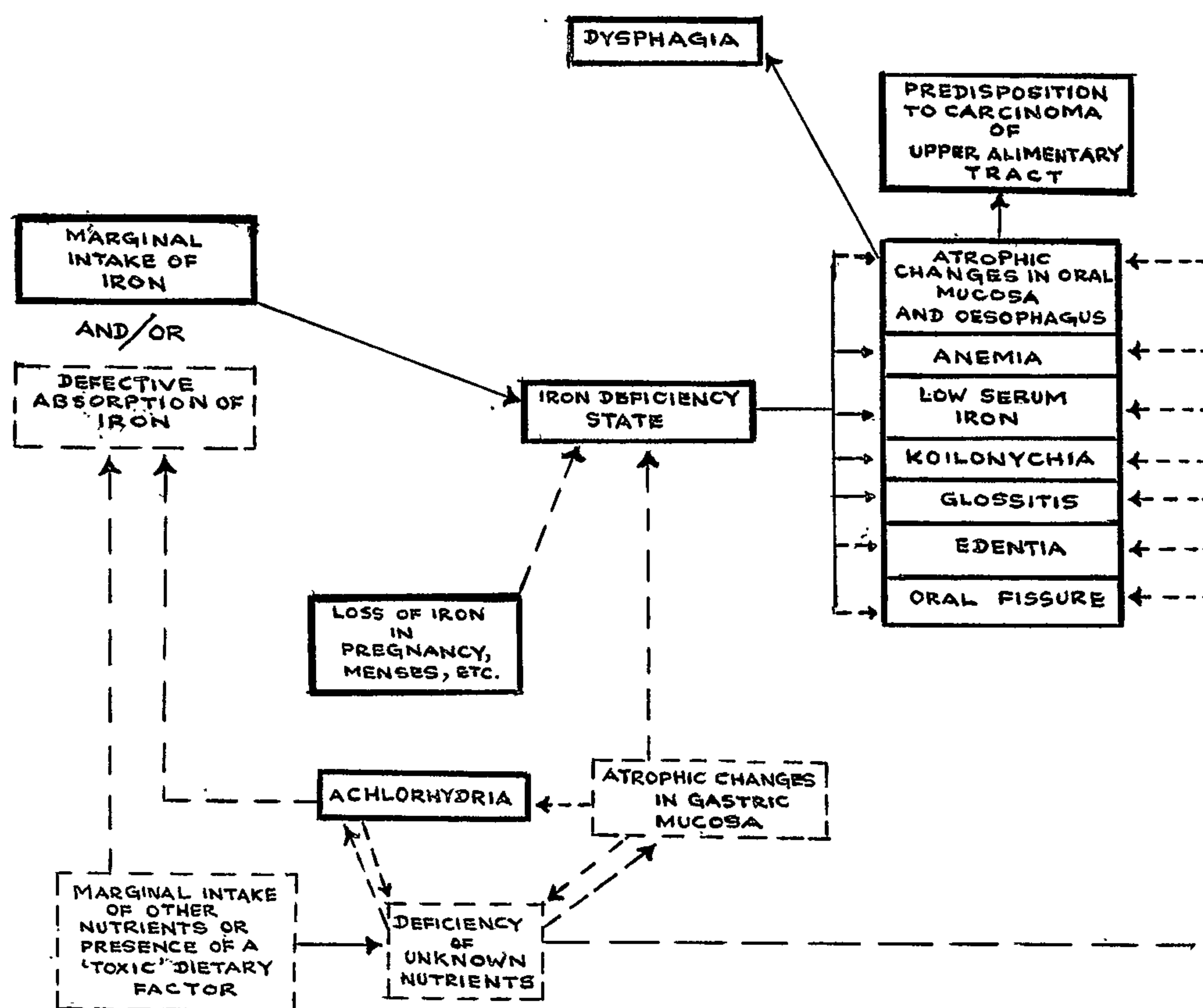
clinical ascorbic acid deficiency in these patients, especially during winter, may be an important factor in reducing the absorption of an already marginal intake of iron. This is based on the established evidence that an increase in ascorbic acid absorption increases iron absorption.

They conclude that possibly the condition is due to a combination of an inadequate intake of iron and a deficiency of the catalytic factors which increase the absorption of iron. The possible relationship between an iron-deficiency state and the development of cancer in the upper alimentary tract is illustrated diagrammatically by them as follows (Figure 4).

According to Castigliano,⁵¹ the diagnosis of Plummer Vinson Syndrome is based on the patient's history and haematologic findings. Uthman³⁸⁰ indicates that this condition should be distinguished from

1. Vitamin B complex deficiency, which would present the same oral picture, but would be excluded by the blood picture.
2. Pernicious anaemia, which can be excluded by blood analysis.
3. Anaemia associated with a malignant lesion in the intestine, which can be excluded by an examination of the stools for the present of occult blood.

Figure 4



*Closed boxes indicate factors known to co-exist in Plummer-Vinson Syndrome.
Solid lines indicate relationships held to be reasonably certain.
Broken lines indicate relationship postulated or theoretically possible.*

DIAGRAMMATIC SCHEME INDICATING POSSIBLE RELATIONSHIPS
BETWEEN IRON-DEFICIENCY STATE AND THE DEVELOPMENT OF
CANCER OF THE UPPER ALIMENTARY TRACT

Source: WYNDER et al.³⁹³

As for the treatment of this syndrome, Lederer and Skolnik¹⁶⁴ indicate that there is no satisfactory treatment except for the administration of large doses of vitamin A, vitamin B complex, and iron. Shafer, Hine and Levy³¹⁸ report that the anaemia usually responds satisfactorily to iron therapy and a high protein diet, while Weisberger³⁹⁰ indicates that the treatment of the anaemia has had no effect on the eventual development of carcinoma.

OTHER ORAL PRECANCEROUS LESIONS

While leukoplakia and Plummer Vinson syndrome have been firmly established as definite precancerous conditions, there is a miscellaneous group of oral lesions which have created a great deal of controversy as to their potential malignant transformation, or their relationship to cancer development. This obscure 'precancerous group' include such lesions as leukoedema, certain types of oral ulcers, pigmentation, papillomas, sub-mucous fibrosis, papillary hyperplasia, intra-epithelial carcinoma, and erythroplasia of Queyrat.

LEUKOEDEMA

Shafer, Hine and Levy³¹⁸ discuss this condition under the heading of premalignant oral lesions, and indicate that it is an abnormality of the buccal mucosa which clinically resembles early leukoplakia. However, they point out that since the etiology of both leuko-

edema and leukoplakia has not been established, analysis of the relationship of these two conditions must await further study. On the other hand, Sharp, Bullock and Hazlet³²³ regard leukoedema as a pre-leukoplakia which is reversible on removal of the causative factors, although in some cases the condition progresses into leukoplakia.

Sandstead and Lowe,³⁵⁴ in an investigation of 105 patients with leukoedema, indicate that the importance of this condition lies in the possible transformation of an area of leukoedematous mucosa into leukoplakia through chronic irritation or trauma. However, they feel that leukoedema by itself is not a dangerous condition. In the same study, they report that the incidence of leukoedema in Negro men (94 per cent.) and women (86 per cent.) was about twice that in white men (45 per cent.) and women (40 per cent.), and that the average age of the patients was 45 years.

Shafer, Hine and Levy³¹⁸ state that the etiology of leukoedema is unknown. The study of Sandstead and Lowe³⁵⁴ reveals no apparent relationship between this condition and the use of tobacco, the pH of the saliva, bacterial infection in the mouth, syphilis, or galvanism from dissimilar metallic fillings.

According to Shafer, Hine and Levy,³¹⁸ the

clinical appearance of leukoedema may take on a filmy opalescence of the mucosa in the early stages, and this may develop into a more definite whitish gray appearance with a wrinkled surface in later stages. In the majority of cases, bilateral involvement of the buccal mucosa is commonly seen, especially along the occlusal line in the bicuspid and molar region. They indicate that microscopically, the epithelium of the involved oral mucosa thickens, and there is intracellular edema of the spinous or malphigian layer with irregularly elongated broad rete pegs and inflammatory cell infiltration of the subjacent connective tissue.

PAPILLOMAS

Lederer and Skolnik¹⁶⁴ indicate that papillomas may occur anywhere in the oral cavity, and their importance clinically is based upon the possibility of their becoming malignant. They differentiate two types of papillomas and regard the inverted type in which there is epithelial downgrowth as precancerous. They quote Ewing as stating that the gradual transformation of a benign papilloma into a malignant tumour has been adequately demonstrated. This view is shared by Halperin,¹²⁹ Rose,²⁸² Castigliano,⁵¹ Hetessy,¹²⁵ and Thoma³⁶⁸ who indicate that malignant degeneration of papillomas is feasible, and they should be regarded as precancerous.

On the other hand, Gorlin^{109*} is of the opinion that papillomas are always benign, and that those cases which had been described as becoming malignant were probably confused with papillary verrucous or exophytic carcinöma. Toto³⁶⁴ indicates that papillomas are generally benign, but they may exhibit acanthosis and, very rarely, dyskeratosis with malignant degeneration, while Shafer, Hine and Levy³¹⁸ express that such a possibility is fairly remote.

Shklar³⁰³ states that it is still somewhat uncertain whether the papilloma should be regarded as premalignant. However, he indicates that evidence of dyskeratosis or cellular atypia has been observed in a relatively large number of papillomas and, in this regard, they should be treated as having malignant potential.

According to several authorities,^{129, 318, 364, 368} clinically, papillomas are exophytic growths with a firm, stalk-like base. However, Lederer and Skolnik¹⁶⁴ indicate that there is an inverted type which is less common than the exophytic type. Papillomas may be pedunculated or sessile and, intraorally, are found on the tongue, lips, buccal mucosa, gingivae, and especially the soft and hard palate. Shafer, Hine and Levy³¹⁸ indicate that most papillomas are small, but occasionally lesions measuring several

centimetres in diameter are encountered. They state that these growths are seen in all ages and sometimes in quite young children.

Histologically, the numerous small finger-like projections, above the surface of the oral mucosa, have a stratified squamous epithelial covering with a central core of connective tissue supporting the blood vessels.^{318, 368}

The consensus of opinion is that papillomas should be treated by surgical excision, including the base of the mucosa into which the stalk or pedicle inserts.^{129, 318} Thoma³⁶⁸ indicates that excision of papillomas is carried out conservatively with two curved incisions which remove a wedge-shaped piece of tissue with the tumour attached. He adds that in small growths, electrosurgery may be used effectively. If the tumour is properly excised or destroyed, recurrence is uncommon.

DECUBITAL ULCERS

The traumatic or decubital ulcer is regarded to possess malignant potential by Knutson.¹⁵⁰ This view is shared by Lederer and Skolnik,¹⁶⁴ Hertz,¹¹² Castigliano,⁵¹ and Thoma.³⁶⁸

Hetessy,¹²⁵ in an investigation of 100 patients with oral ulcers of various types, estimates that malignant transformation is less than one per cent. He indicates that although the possibility of

malignant degeneration cannot be ruled out completely in individual patients, it is unjustified, in the overall view, to regard an oral ulcer as a premalignant lesion.

Shafer, Hine and Levy³¹⁸ indicate that such ulcers, especially on the lateral borders of the tongue, may strongly resemble carcinoma; but apparently they regard these lesions as mere physical injuries of soft tissues, resulting from longstanding trauma and pressure from dental disorders such as sharp, broken down teeth, ill fitting dentures, etc. Besides the tongue, decubital ulcers are also seen on the buccal mucosa, the lips and, occasionally, on the palate.

PAPILLARY HYPERPLASIA (PAPILLOMATOSIS)

Hertz¹¹² and Robinson²⁷⁵ are of the opinion that papillary hyperplasia should be regarded as pre-cancerous, while Lambson¹⁷⁷ and Shafer, Hine and Levy³¹⁸ indicate that because of its malignant potential, this condition should not be considered as entirely harmless. Thoma³⁶⁸ reports of a case in which a well advanced carcinoma developed from this condition.

The consensus of opinion is that papillary hyperplasia is associated with ill-fitting dentures and poor oral hygiene.^{112, 275, 318} Lambson¹⁷⁷ surveyed 226 denture wearing patients and reports that the prevalence of this condition was 11 per cent. He

indicates that relief areas in denturs initiate papillary hyperplasia, and that there is a definite relationship between this condition and the wearing of dentures day and night. Because many persons who have ill-fitting dentures and yet do not develop papillomatosis, Shafer, Hine and Levy³¹⁸ believe that there must be some unidentified factors which predispose to this condition.

Clinically, the papillary lesion is red, sessile, and presents itself as numerous papillary projections above the mucosa, or it may exhibit a nodular or raspberry-like surface.^{177, 318} The surface morphology of another type of papillary hyperplasia is mossy or velvet-like.¹⁷⁷

According to Shafer, Hine and Levy,³¹⁸ histologically, the numerous projections each has a stratified squamous epithelial covering and a central core of connective tissue. They share with Robinson²⁷⁵ the opinion that hyperkeratosis and dyskeratosis may be present, and according to the latter author, frank malignancy is occasionally encountered.

In the treatment of papillary hyperplasia, Thoma³⁶⁸ indicates that electrosurgical excision has proved to be most satisfactory in the majority of palatal lesions. In very extensive cases, he advocates the entire removal of the involved mucosa by means of

a periosteal elevator following an incision around the periphery.

Robinson²⁷⁵ and Shafer, Hine and Levy³¹⁸ recommend conservative treatment first, that is, discontinue using the ill-fitting denture, and if there is no regression of the lesion, then surgical excision is carried out.

INTRAEPITHELIAL CARCINOMA

This condition, also known as Bowen's disease and carcinoma-in-situ, has been included under the discussion of oral precancerous lesions by Shafer, Hine and Levy.³¹⁸ They indicate that some authorities are of the opinion that this is a laterally spreading intraepithelial type of superficial epithelioma or carcinoma, while others believe that it merely represents a precancerous dyskeratotic process.

Pindborg²⁵¹ states that Bowen's disease is a rare condition and, unlike leukoplakia, it is always precancerous when found in the oral cavity. He indicates that the epithelium is the seat of an atrophy and exhibits varying degree of cellular atypia.

According to Shafer, Hine and Levy,³¹⁸ clinically the lesion may appear as an erythematous, velvety plaque which may or may not be raised, while histologically it is characterised by hyperkeratosis,

acanthosis and dyskeratosis. They indicate that there is no uniformity in the treatment of this lesion, surgical excision, radiation, and cautery all have been used. If left untreated, carcinomatous invasion inevitably results.

ERYTHROPLASIA OF QUEYRAT

It has been pointed out that this disease was originally described by Queyrat in 1911 in the glans penis of a syphilitic patient, but since then similar lesions have been reported to occur on the vulva and the oral mucosa.^{106, 318}

Shafer, Hine and Levy³¹⁸ indicate that essentially this is an intraepithelial carcinoma, except that invasion of the underlying tissues occur earlier. On the other hand, Hertz¹¹² regards this condition as a precursor of leukoplakia and indicates that it is frequently mistaken as such.

Sprague³⁰⁶ identifies a group of oral mucosal lesions of a precancerous (or microscopically malignant) nature, and is of the opinion that clinically, this group resembles erythroplasia of Queyrat which he believes is a carcinoma-in-situ.

According to Shafer, Hine and Levy,³¹⁸ clinically there is nothing characteristic about erythroplasia of Queyrat, the lesions may appear as single, well-defined patches with a bright red, velvety

surface, while histologically they exhibit features similar to those seen in intraepithelial carcinoma.

ORAL PIGMENTATION

Paymaster,^{241, 242} in his study of Indian patients with oral cancer, noted a casual relationship of the occurrence of intraoral malignancy and the frequency of pigmentation in the mucous membranes of the mouths of these patients. He observed that only five per cent. of the normal healthy adult population exhibits scattered areas of pigmentation of the oral and pharyngeal mucous membranes, while in patients with cancer of the oral cavity and pharynx, this form of pigmentation is five times more frequently seen. He indicates that the significance of this is not known at present, but it merits further investigation.

In a discussion of pigmented nevi, Shafer, Hine and Levy³¹⁸ point out that the "junctional activity" displayed by junctional nevi has serious implications, since this form of nevi frequently undergo malignant transformation into melanomas.

Hertz¹¹² indicates that the so-called pigmented nevus (nevus pigmentosus) may be the point of departure of malignant melanomas, while Castigliano⁵¹ expresses the belief that although the incidence of malignant degeneration of any given pigmented mole is exceedingly low, they sometimes do give rise to malignant melanomas.

ORAL SUBMUCOUS FIBROSIS

Pindborg^{251, 260} indicates that this oral condition, described by Joshi in 1953, is seen mainly among Indians, although its occurrence in Ceylon, Malaysia, Nepal, South Vietnam, and Thailand has been noted. Its importance as a precancerous condition in the oral cavity has been established by the findings of Pindborg,^{251, 260, 262} Pindborg and Zachariah,²⁶¹ Pindborg et al.,^{263, 264} Paymaster,²⁴¹ Paymaster and Gangadharam,^{242, 253} and Rao.²⁸⁴

An epidemiological survey of oral submucous fibrosis among Indian patients in Bombay and Lucknow was conducted by Pindborg,^{260, 262} and his findings are tabulated as follows (Table 15).

In another investigation of this condition in South India, Pindborg and Zachariah²⁶¹ report that in 100 patients with intraoral carcinoma, 40 (40 per cent.) had clinical signs of submucous fibrosis as compared to 19 (less than one per cent.) who had submucous fibrosis among 2,000 persons with no oral malignancy.

Rao,²⁸⁴ in a study of 46 cases, reports that most of the patients were in the second decade of life, the youngest patient was 12 years old and the oldest 64 years of age. There were 29 women and 17 men in the group.

The findings of Paymaster and his associates

TABLE 15

RESULTS FROM EPIDEMIOLOGICAL SURVEYS OF ORAL SUBMUCOUS FIBROSIS IN BOMBAY AND LUCKNOW

	Bombay	Lucknow
Individuals	10,000	10,000
Number with submucous fibrosis	50	51
Percentage with submucous fibrosis	0.50	0.51
Ratio men:women in submucous fibrosis	3.2:1	1.3:1
Average age for men with submucous fibrosis	44.3 yrs	47.5 yrs
Average age for women with submucous fibrosis	38.8 yrs	37.6 yrs
Percentage Cases with concomitant leukoplakia	38.0	15.7
Percentage cases with concomitant carcinoma	2.0	9.8

Source: PINDBORG^{260, 262}

241, 242, 253 indicate that oral submucous fibrosis affects mainly the hard and soft palate, and the tonsillar fossa. On the other hand, Pindborg,²⁶² in his study of 40 patients with this condition, reports that the cheeks were most frequently affected, with the tongue next, and the gingiva and floor of the mouth rarely involved.

The cause of oral submucous fibrosis is unknown, although Sirat and Khanolkar (quoted by Pindborg^{260, 261})

suggest that the irritating effect of chilli may give rise to this condition. They indicate that capsaicin, the active ingredient in chilli, has been shown to cause a connective tissue response in the rat's palate similar to the changes in submucous fibrosis in man.

According to Rao,²⁸⁴ submucous fibrosis may be a manifestation of disordered growth of collagen. Pindborg^{260, 262} indicates that the basic change in this condition is a fibro-elastotic transformation of the lamina propria connective tissue with epithelial atrophy, and is occasionally preceded by vesicle formation. As the fibrosis progresses, the oral mucous membrane exhibits stiffness, and trismus eventually occurs which may cause difficulties in chewing, swallowing and speaking.

Rao²⁸⁴ indicates that the salient features in the symptomatology of patients with this condition include the inability of patients to open their mouth, to tolerate pungent food, to blow out a candle, or to whistle. Mobility of the tongue is impaired, and pain in the ears, lower jaw, and neck frequently accompanies swelling of the lower jaw and neck. On palpation, the cheeks feel tough and markedly thickened, and the soft palate has a hard, rubbery feeling with restricted mobility. Paymaster^{241, 253} indicates that

patients frequently complain of a severe burning sensation in the affected area, and in about 30 per cent. of cases, a slowly growing squamous cell carcinoma develops in the affected site.

In the series studied by Pindborg et al.,²⁶³ the hematologic findings showed an increased erythrocyte sedimentation rate and a mild neutropenia. Anemia was present in about 40 per cent. of the patients, and this corresponds to the findings of Rao,²⁸⁴ but in contrast, a peripheral eosinophilia was not significant in Pindborg's²⁶³ findings.

With regard to treatment of this condition, Pindborg et al.²⁶³ indicate that several methods of therapy have been tried which include surgical cutting of the fibrotic bands, and/or injection of fibrolysia, gold, or vitamins A and E. Rao²⁸⁴ states that cortisone and its latest purified derivatives have met with some success, and these have been administered in local injections, tablets, and by systemic injections.

HISTOPATHOLOGY AND GRADING OF ORAL CANCERHISTOPATHOLOGY

Squamous cell carcinoma is the most common form of malignant neoplasms encountered in the oral cavity. According to various authorities,^{14, 16, 28, 51, 79, 105, 106, 119, 165, 170, 288, 398} this histologic type of cancer represents about 90 per cent. of all oral malignancies. Castigliano⁵¹ states that malignant tumours of salivary gland origin (adenocarcinoma, mixed tumour, etc.) and the occasional oral sarcomas make up nearly all the remainder. Therefore, as can be seen, the real problem of malignancy of the oral cavity is that produced by squamous cell carcinoma and, for this reason, only the histopathologic features of this form of cancer will be considered in this discussion.

The following histologic description of squamous cell carcinoma is adapted from Shafer, Hine and Levy.³¹⁸ They indicate that although the histologic picture of intraoral squamous cell carcinoma varies from case to case, in general, they are moderately well differentiated neoplasms; exhibiting a certain degree of keratinization.

The well differentiated squamous cell carcinoma generally consists of large cells with distinct cell membranes, and are arranged in sheets and nests,

bearing a resemblance to squamous epithelium. The nuclei of these neoplastic cells are large, and they exhibit various degree of hyperchromaticity. In well differentiated epidermoid carcinoma, mitotic figures, which are atypical, are not especially numerous, but one of the most prominent features is the presence of individual cell keratinization and the formation of numerous epithelial pearls of varying size.

In the less well differentiated squamous cell carcinoma, the resemblance to squamous epithelium is less pronounced. The shape of the cells, their typical arrangement one to the other, and their growth rate may be altered. Mitotic figures are more numerous, reflecting an increased proliferative activity, but there is less keratin formation.

The poorly differentiated epidermoid carcinoma bears very little resemblance to its cell of origin. The growth rate of the individual neoplastic cells is very rapid and this is reflected in the numerous mitotic figures present. These cells exhibit an even greater lack of cohesiveness and are extremely vagarious, actively invading the adjacent connective tissue.

GRADING

The varying degrees of differentiation, as

seen in epidermoid carcinoma, is utilised by Broders⁴⁰ in the microscopic grading of cancer. In this classification, he distinguishes four grades of tumours as follows:

GRADE 1. The most slowly growing type of tumour with a low grade of malignancy in which differentiation of the cells ranges from 100 to 75 per cent., and undifferentiation from 0 to 25 per cent.

GRADE 2. A carcinoma in which differentiation ranges from 75 to 50 per cent., and undifferentiation from 25 to 50 per cent.

GRADE 3. The differentiation of cells in this grade ranges from 50 to 25 per cent., and undifferentiation from 50 to 75 per cent.

GRADE 4. A rapidly growing carcinoma in which differentiation ranges from 25 to 0 per cent., and undifferentiation from 75 to 100 per cent.

Broders⁴⁰ points out that the value of such a microscopic grading lies in determining the prognosis and treatment of malignant tumours in general. He indicates that, generally speaking, the grades of malignancy of carcinomatous growths are directly proportional to their proliferative, infiltrative, metastasizing, and death-dealing capacities. He adds that technical and anatomic factors being equal, the radiosensitiveness of

cancer, in general, is in direct proportion to its grade of malignancy.

Shafer, Hine and Levy³¹⁸ indicate that a major shortcoming in such a grading is that the same tumour may show different degrees of differentiation in varying areas and, therefore, varying degrees of malignancy. This serious disadvantage has prompted the discontinuance of this grading system and, instead, most pathologists now modify the diagnosis of the neoplasm by a descriptive adjective, indicative of its differentiation.

Ueno³⁷² points out the serious shortcomings of Broders' grading, and presents the following system of grading based on the clinical course of the disease:

GRADE I. Primary growth limited in extent to the site of origin. There is no loss of mobility or function, and no palpable nodes.

GRADE II. Primary growth spreading to adjacent structures. No palpable nodes.

GRADE III. Primary growth as in I and II. Regional lymph nodes are invaded, but are mobile and confined to area of immediate lymphatic drainage.

GRADE IV. Primary growth is too advanced for treatment. The involved lymph nodes are fixed, matted, or distant metastasis has occurred.

Another system of grading malignant tumours, as pointed out by Thoma,³⁶⁸ is that of Warren. According to this classification, three grades are recognized:

GRADE 1. is the best differentiated, probably fairly resistant to radiation, slow to metastasize, and of fairly long clinical course without a tendency to establish metastases.

GRADE 2. is moderately sensitive to radiation, apt to metastasize to regional lymph nodes and sometimes beyond.

GRADE 3. is the least differentiated histologically and is likely to be sensitive to radiation. It is highly malignant and may recur in a radio-resistant form. It often metastasizes widely and the prognosis is relatively poor.

Ash,⁶ in his study of oral cancer utilises two grading systems - the Richards Classification and the system proposed by the International Union Against Cancer using a TNM nomenclature. The two systems are basically and essentially the same in which the primary and secondary lesions are staged separately as follows:

THE RICHARDS CLASSIFICATION

1. PRIMARY LESION

- Stage I - A unilateral or single lesion measuring not more than 1.5 cm. in diameter.
- Stage II - A lesion not larger than 3 cm. in diameter with a corresponding degree of ulceration or infiltration.
- Stage III - A lesion greater than 3 cm. and/or invading adjacent structures.
- Stage IV - A lesion characterized by massive involvement of the region and gross extension to adjacent structures or bone.

2. SECONDARY INVOLVEMENT

- Stage I - Small, discrete, movable, unilateral, operable.
- Stage II - Larger, up to the size of olives, still discrete, unilateral, or lymph nodes as described in (I), but which are bilateral, operable.
- Stage III - Massive metastatic carcinoma in lymph nodes, matted and immovable, may be unilateral or bilateral, inoperable

U.I.C.C. PROPOSAL FOR TNM CATEGORIES, ORAL CAVITY

- T - Primary tumour
- T₁ - Tumour of 1 cm. or less in its greatest dimension
 - Limited to one region - mobility not affected
- T₂ - Tumour more than 1 cm. but not more than 2 cm. in its greatest dimension
 - Limited to one region - mobility not affected
- T₃ - Tumour more than 2 cm. but not more than 5 cm. in its greatest dimension
 - or tumour invading more than 1 region
 - or tumour invading muscle with limitation of mobility
- T₄ - Tumour of more than 5 cm. in its greatest dimension
 - or tumour invading organs or bone

- N - Regional lymph nodes
 - N₀ - No regional lymph nodes palpable
 - N₁ - Homolateral lymph nodes palpable, but movable
 - N₂ - Contralateral or bilateral lymph nodes palpable but movable
 - N₃ - Fixed lymph nodes

 - M - Distant metastasis
 - M₀ - No evidence of metastasis
 - M - Distant metastasis present
-

Castigliano⁵¹ states that almost no all-inclusive classification for oral carcinoma can be defended with any great or lasting ardour. He presents the following classification of the extent of oral malignancy, based on the status of the local disease and the metastatic process:

LOCAL LESION

- Stage 1. Under 1 cm.
- Stage 2. 1.0 cm. to 2.5 cm. in large diameters and confined to local anatomic site, viz., tongue, palate, floor of mouth, etc.
- Stage 3. 2.5 cm. to 4.0 cm. in one long dimension.
- Stage 4. Over 4 cm.

METASTATIC LESION

- "O" : No metastasis
- "A" : Single node, freely movable
- "B" : Two or three contiguous nodes, movable
- "C" : Bilateral nodes or multiple unilateral nodes
- "D" : Fixed mass of nodes
- "E" : Visceral metastasis.

METASTASES

The ability to metastasize, both locally and to a distance, is one of the important characteristics of malignant tumours. According to Boyd,²⁶ the spread of cancer cells may occur by six methods:

1. by infiltration of tissue spaces
2. by the lymphatic system
3. by the blood stream
4. along natural passages
5. through serous cavities
6. by innoculation

Lee McGregor²²⁵ indicates that the age of the patient is important with regards to the spread of tumours. This is because the lymphatic system displays its greatest activity during childhood and youth and, with increasing age, there is a slower rate of lymph node involvement following malignancy.

REGIONAL (LOCAL) LYMPH-NODE METASTASES

Copeland⁷¹ states that cancer about the head and neck spreads mainly by lymphatic pathways with the exception of certain types which have a relatively high incidence of vascular metastases. He indicates that the majority of malignant tumours arising in this region of the body tend to spread unilaterally through tumour emboli to regional lymph nodes, and usually a group of lymph nodes will have become involved

before they are clinically noticeable. Bilateral metastases are predictable if the primary tumour is located near the midline, extends across the midline, or if sufficient lymphatic blockage occurs on one side of the neck to accelerate retrograde extension across the neck.

According to Wookey et al.,⁴¹¹ the lymph nodes which may be involved in oral cancer are those of the submaxillary, submental, or deep cervical groups. They indicate that in intraoral lesions, metastases involve primarily the nodes of the deep cervical group. On the other hand, Shafer, Hine and Levy³¹⁸ state that metastases from intraoral carcinomas chiefly involve the submaxillary, and superficial and deep cervical lymph nodes, although occasionally the submental, preauricular, postauricular, and supraclavicular nodes are involved. They add that the spread is by lymphatic routes mainly and blood stream metastasis from oral cancer is uncommon. The routes of lymphatic spread in the head and neck is well documented by Lee McGregor.²²⁵

Castigliano⁵¹ states that all cases of intraoral malignancy metastasize freely, especially in malignant melanomas and in squamous cell carcinomas involving the tongue, floor of the mouth, and soft palate. However, he and Martin¹⁸⁰ are of the opinion that metastasis generally occurs only after the primary cancer in the mouth has been present for some

time - a few weeks at least. The chances of metastasis occurring increases proportionately with the patient's delay in seeking treatment.

Paymaster²⁴¹ indicates that the mobility of the part seems to be a significant contributing factor in hastening the spread of tumour cells to the lymph nodes. Thus, the incidence of cervical metastasis has been observed to be higher from the mobile tongue, the floor of the mouth, and the soft palate than from the alveoli and the hard palate. Similarly, the incidence of cervical metastasis is significantly lower from cancer involving the anterior two-thirds of the buccal mucosa than from those of the posterior one-third, and he attributes this difference to the activity of the masseter muscle (which is located in the posterior one-third region of the buccal mucosa) since the movements of this muscle during mastication may have contributed to the dissemination of tumour cells.

From a review of the literature, the reported incidence of cervical metastasis in patients with oral cancer ranges from about 29 per cent. to 63 per cent. The findings of different investigators are tabulated as follows (Table 16).

TABLE 16

INCIDENCE OF CERVICAL LYMPH NODE METASTASES IN PATIENTS
WITH ORAL CANCER

Author	Total Number of Patients	Cervical Metastasis		Remarks
		No.	%	
GARDNER, LOVE and HAMBURGER ¹⁰⁵	189	-	49.5	
GARDNER ¹¹⁷	167	-	51	
SIMONS, MASSON and BEAHR ³⁵²	150	79	53	histologically proved
MUSTARD and IRVING ²¹⁸	1,177	630	53.6	either clinical or pathologic evidence
LEFFALL and WHITE ¹⁶⁵	107	68	63	
WOOKEY et al. ⁴¹¹	1,963	572	29.1	
COGBILL ⁷³	82		50	microscopic evidence

DISTANT METASTASES

Rubenfeld, Kaplan and Holder²⁷⁸ define distant metastases as growths which arise from but are not continuous with the primary tumours. They add that involved cervical lymph nodes draining the original site are not covered by this term. Others^{138, 363} indicate that the term "distant metastasis" in cancer of the oral cavity and adjacent region of the head and neck implies the dissemination of the disease to

organs or tissues below the level of the clavicle.

Lucas¹⁷⁰ and Gowen and de Suto-Nagy¹²⁰ indicate that the once popular belief that malignancy of the mouth and adjacent region does not metastasize below the clavicle is untrue. It is the opinion of Topazian³⁶³ that early reports of the low incidence of distant metastasis from oral cancer (1 per cent.) may have been based only on clinical evidence without autopsy findings. On the other hand, Castigliano⁵¹ ascribes this to a probable general lack of interest in advanced and terminal cases of oral malignancy in which distant metastasis is found. He also feels that with improved methods of treatment employed today for advanced cases, the patients' lives may be prolonged and, thus, allowing more opportunity for distant metastases to take place.

Martin¹⁸⁰ states that in uncontrolled cancer of the mouth, metastasis invariably occurs to some viscus below the clavicles such as the lungs, liver, or bones. Hoyer¹³⁸ indicates that a certain percentage of patients with head and neck cancers have distant metastases at the time of death, and this is substantiated from his review of the literature, the findings of which are tabulated as follows (Table 17).

TABLE 17

THE REPORTED INCIDENCE OF DISTANT METASTASES IN PATIENTS
DYING WITH EPIDERMOID CARCINOMA OF THE HEAD AND NECK AREA

Author	Year Report	Site of primary lesion	No. of pat- ients	Patients with dist. metast.	
				No.	%
AUTOPSY STUDY			857	177	20.6
KETTLE	1916	Tongue, Mouth, lip, oral cavity, pharynx	43	6	13.9
WILLIS	1930	Lip, oral cavity, broch- iogenic	20	10	50.0
PRICE	1934	Laryngo-pharynx, lip, tongue, larynx	94	10	10.6
BURKE	1937	Antrum pharynx, lip, skin, oral cavity	54	14	25.9
WILLIS	1941	Larynx, pharynx, sinuses	64	25	39.0
BRAUND and MARTIN	1941	Sinuses, pharynx, lip, oral cavity	223	42	18.8
PELTIER et al.	1951	Sinuses, base of tongue	177	31	17.3
AURIOL and PAPILAN	1959	Laryngo-pharynx	182	39	21.4
CLINICAL and AUTOPSY STUDY			599	36	6.1
CASTIGLIANO and ROMINGER	1954	oral cavity	321	17	5.3
PERZIK et al.	1958	Tongue, floor of mouth	278	19	7.0

Source: HOYE¹³⁸

From his own autopsy study of 42 patients who died of epidermoid carcinoma of the head and neck, Hoyer¹³⁸ reports that 23 (55 per cent.) were found to have distant metastases. This parallels the findings of Gowen and de Suto-Nagy,¹²⁰ who report that 35 (57 per cent.) of 61 patients with malignancy of the head and neck had distant metastases on autopsy. The two studies emphasize the need for a thorough search for distant metastases when an operation is contemplated in patients with advanced head and neck carcinoma. Other published reports by different investigators regarding distant metastatic spread in patients with cancer of the oral cavity and adjacent head and neck region are summarized as follows:

WARD, EDGERTON and CHAMBERS (1959)⁴¹² - of 577 patients with carcinoma of the oral cavity (exclusive of lip), 12 had distant metastases when first seen, representing about 2 per cent.

TOPAZIAN (1961)³⁶³ - Of 83 cases of oral cancer in which autopsies were performed, distant metastatic lesions were found in 20 (24 per cent.) of the patients.

ARONS and SMITH (1961)¹² - Of 89 patients with cancer of the head and neck, 21 per cent. developed X-ray evidence of distant metastatic involvement of the lungs and bone.

RUBENFELD, KAPLAN and HOLDER (1962)²⁷⁸ - Of 132 patients with malignancy of the head and neck observed over a five year period, the incidence of distant metastasis based on clinical evidence was 21 per cent.

GARDNER, HAMBURGER and LOVE (1963)¹⁰⁵ - Of 189 cases of oral malignancy, 14.8 per cent. exhibited distant metastases.

COLEMAN (1965)⁷² - The incidence of distant metastasis in a highly selected group of 78 patients with advanced cancer of the tongue, floor of the mouth, buccal mucosa, tonsillar fossa, and hypopharynx was about 10 per cent.

COGBILL (1965)⁷³ - Of 94 patients who died of intraoral cancer and in whom autopsies were performed, 54 or 57.4 per cent. were found to have metastases beyond the clavicle.

Martin and his associates,^{197, 198, 200, 201} reporting on the frequency of distant metastasis from cancer of the tongue, floor of the mouth, buccal mucosa, and gingiva observed that distant metastatic spread was found in approximately 12 per cent. of 556 cases of lingual cancer, 1 per cent. of 103 cases of cancer of the floor of the mouth, 2 per cent. of 99 cases of cancer of the buccal mucosa, and 5 per cent of 113 cases of gingival cancer.

From this, it can be seen that there is a great divergence in the reported incidence of distant metastases in cancer of the oral cavity and the adjacent region of the head and neck. Each report should be examined in the light of its publication date, since the earlier reports seem to under estimate the frequency of this phenomenon. Also, in studying the various reports, care must be taken to see whether the findings are based on autopsy or clinical evidences. Castigliano and Rominger⁶⁶ feel that it would be more rational to report cases of distant metastases on the basis of total experience rather than on autopsy experience. They indicate that by so doing, a clear conception of the small part that distant metastases play in oral cancer can be obtained. They add that remote metastatic spread can be accurately diagnosed by sound clinical judgement and a thorough knowledge of the behaviour pattern of oral malignancy.

On the other hand, Gowen and de Suto-Nagy¹²⁰ maintain that clinical and roentgenographic examinations would not suffice in evaluating the frequency of distant metastases. They feel that an autopsy provides the fullest opportunity to examine all sites of metastases and, therefore, an accurate estimate of the incidence of distant metastases.

Topazian³⁶³ states that the pathogenesis of remote metastasis from cancer of the oral cavity

involves the invasion of the walls of blood vessels, mainly the veins. Boyd²⁶ indicates that the veins are invaded with greater ease than the arteries, and this appears to be due to the frequent penetration of the walls of the larger veins by lymphatics, forming a plexus reaching the sub-endothelial region, whereas this is not so in the arteries. He states that a thrombus forms over the eroded endothelium, which is invaded by tumour cells and it is this combination of thrombus and tumour which becomes detached to form the tumour emboli that are likely to result in metastases.

Topazian,³⁶³ quoting other investigators, indicates that the majority of arrested emboli, which have been carried to distant sites do not develop metastatic lesions, and that certain favourable conditions for the migration and growth of the emboli must be present. He quotes Berenblum as stating that tissues receiving the emboli must be capable of rapidly providing a blood supply for the new tumour tissue which, in turn, must be capable of withstanding the period before vascularization. He adds that only tumour cells at the stem-cell level have the potential of successful distant metastatic spread, since mature cells would not multiply and proliferate.

There appears to be a predilection for certain

distant sites in visceral metastases from head and neck cancer. Thus, in the studies of Gowen and de Suto-Nagy,¹²⁰ Topazian,³⁶³ and Castigliano and Rominger,⁶⁶ the lungs were the most common sites of distant metastases, and next was the liver. Similarly, Arons and Smith,¹² and Rubenfeld, Kaplan and Holder²⁷⁸ report that the lungs were the most frequently involved sites in their studies, with the bones next. Other reported distant sites were the pleura, hilar lymph nodes, chest wall, thyroid gland, abdominal lymph nodes, adrenal glands, kidneys, diaphragm, axillary lymph nodes, spleen, heart, esophagus, and small intestines.

Gowen and de Suto-Nagy¹²⁰ indicate that distant metastases arose most frequently from cancer of the tongue, pharynx, and larynx, while in the study of Topazian,³⁶³ carcinoma of the tonsils, floor of the mouth, palate, and tongue had the greatest tendency to remote metastatic involvements. The former investigators report that 70 per cent. of the primary tumours with distant metastases were in grades II and III, as compared to 90 per cent. in grades I and II in those without distant spread. Similarly, Topazian³⁶³ indicates that among the tumours which produced distant metastases, 35 per cent. were differentiated as grade III and 5 per cent. were classified as grade I, as compared to 17 per cent. grade III tumours and

13 per cent. grade I tumours in those which did not display remote metastasis. Hoyer¹³⁸ is of the opinion that the grade of the primary tumour has some correlation with the subsequent development of distant metastases.

Topazian³⁶³ states that in general, the metastases tend to reproduce the histologic structure of the primary tumour, while Gowen and de Suto-Nagy¹²⁰ indicate that frequently the metastases are less differentiated than the primary tumour.

THE GENERAL TREATMENT OF ORAL CANCER

A review of the literature shows that there is considerable divergence of opinion in the treatment of intraoral malignancy. Many surgeons still hold the opinion that surgery is the best form of therapy for technically operable oral cancer. On the other extreme, many radiotherapists still regard the treatment of cancer of the mouth as an exclusively radiological problem. Thoma³⁶⁸ feels that a close co-operation of the surgeon, the radiotherapist, and the pathologist is essential in the treatment of this disease.

James^{141, 145} indicates that the choice of treatment, whether radiologically or surgically, is determined by factors such as location of the lesion, histologic type, age of the patient, previous treatment, the extent of involvement, the general physical condition of the patient, and whether the lesion is primary or metastatic. He is of the opinion that surgery or radiation therapy are equally effective in the treatment of small primaries. Quite frequently a combination of surgery and radiotherapy are employed.^{114, 219}

Murray et al.²¹⁹ indicate that apart from surgery and radiotherapy, electrocoagulation and

chemotherapy are standard methods in the treatment of primary lesions. Chemotherapy has come to the fore only recently and, at present, is still mainly used on a palliative basis. Boyd²⁶ points out that it is impossible to avoid the destruction of normal tissue whichever method is used, and the ideal therapeutic agent would be one with a selective action on and an affinity for malignant cells while leaving normal cells untouched.

SURGERY

Surgery was the first effective method in the treatment of cancer. In oral malignancy, surgery may range from a local excision of a tumour to a radical en bloc resection to include the primary lesion, the adjacent bone, and cervical lymph nodes.¹⁸³ Murray et al.²¹⁹ indicate that the treatment of head and neck cancer often affects the functions of chewing, swallowing, speaking and breathing and, for this reason, any technique to minimize disability without impairing the therapeutic effectiveness is the treatment of choice. Several authorities^{51, 72, 141, 330, 368} are of the opinion that in many instances fairly radical surgery is essential to effect a cure. They and Beahrs and Barber⁴¹ believe that the ideal operation for any malignant lesion is one which widely extirpates the lesion with a generous margin of normal tissue, since the first attempt to resect a tumour offers the

best opportunity for control.

In the past, radical surgery was not encouraged because of the high incidence of postoperative infection, delayed wound healing, and post-anaesthetic pulmonary complications. However, with the advent of endotracheal anaesthesia, refined transfusion procedures, and a combination of sulfa drugs and antibiotics, the best results of radical surgery are more encouraging. Ward and Chambers⁴¹⁰ indicate that operative mortality and morbidity has been reduced to such an extent as to make radical surgery for mouth cancer practicable. According to various authorities^{41, 72, 73, 85, 352, 412} the surgical mortality ranges from 1.5 per cent. to 11 per cent.

Simon, Masson and Beahrs³³⁰ are of the opinion that radical surgery offers the patient with extensive intraoral cancer the best chance of a cure. This is supported by the favourable results they obtained in the treatment of 150 patients with this disease by radical surgery.

Ward and Chambers⁴¹⁰ indicate that radical surgery should be aimed at two goals,

- removal of the primary tumour along with the primary pathways of lymphatic spread
- the cosmetic and functional rehabilitation of the patients.

Sometimes a cure of the disease can only be achieved with great sacrifice of the cosmetic appearance functional disability of the involved region. In such cases, cosmetic reconstruction should be contemplated after the disease is definitely under control, plus the restoration of function wherever possible.²²⁰ Des Prez et al.⁸⁵ indicate that total immediate reconstruction at the time of surgical excision is an integral part of the operative procedure.

Surgical accessibility is necessary for adequate removal of the lesion. Martin,³⁵³ a strong advocate of surgery in the treatment of head and neck cancer, indicates that in some anatomic sites such as the nasopharynx, because of surgical inaccessibility, the lesion must be treated by irradiation. He and James¹⁴¹ share the opinion that certain tumours, located in the posterior region of the oral cavity, are radiosensitive and are best treated by radiotherapy. According to the former author, the selection of treatment method must nevertheless always be made on the basis of which offers the best chance of cure.

The consensus of opinion is that residual or recurrent cancer, following radiation therapy, is best treated by surgery. McLaren²²⁰ indicates that in operable cases, recurrent or residual tumours and

previously irradiated tissues are excised en bloc with as much a normal margin of tissue as possible, regardless of crossing normal anatomical planes. He adds that a reasonable prospect of cure of the disease must exist, and patients should not be exposed needlessly to mutilation and multiple reconstructive procedures.

RADIOTHERAPY

With a tradition of about fifty years, radiotherapy is a relative newcomer in the field of cancer therapy. Recent refinements in radiotherapy increase the usefulness of this type of treatment for oral cancer. The aim of all modern radiotherapy is to deliver a dose which will have maximum destructive effect upon the neoplastic cells, with the minimum danger to normal tissues through adequate filtration and graduated exposure.

Radiotherapy depends for its action on the biological response to ionizing radiation.²⁸⁶ The effectiveness of ionizing radiation on malignant neoplasms depends on selective damage to malignant cells. This implies greater sensitivity of tumour cells than of normal tissue cells, this difference in vulnerability being exploited in therapeutic practice.

James¹⁴¹ indicates that sufficient radiation should be delivered to the tumour on the initial

treatment, as radiation failures are frequently due to a sublethal dosage or mis-directed beams. He states that careful consideration should be given to the choice of the many modalities of radiotherapy in each individual case of intraoral malignancy. X-ray irradiation in high and low voltage, radium, radon, Co^{60} , Ir^{192} , and Au^{198} can all be used to the best advantage in appropriate situation.

According to James,¹⁴¹ low voltage therapy is employed for surface lesions and high voltage when deep penetration is desired. Radium and other isotopes can be used in moulds for contact therapy, and implants of radon or gold¹⁹⁸ are frequently used to supplement external high voltage therapy. Delclos⁸⁶ indicates that a high dose can be delivered to the tumour without unnecessarily irradiating a large volume of normal tissue by the use of radioactive sources in moulds. According to him, moulds should be light, comfortable to the patient with a certain degree of rigidity and immobility, and constructed so that normal tissue will be at a greater distance from the radioactive source than will the surface to be treated. Pointon²⁶⁷ indicates that this type of treatment is very suitable for anterior lesions arising in the floor of the mouth with minimal tongue involvement.

Declos⁸⁶ is of the opinion that when limited

in extent, malignancy of the anterior two-thirds of the tongue, floor of the mouth, and buccal mucosa may be controlled by implants such as radium needles or by afterloading cannulas with iridium and tantalum wires, cesium rods, and other similar radioactive sources. He advocates the use of external irradiation for larger tumours, and also for tumours of the retro-molar trigone, soft palate, and the lower and upper gums. Pointon²⁶⁷ indicates that radium techniques, whether by means of implants or the use of intraoral applicators, enable a high dose to be strictly confined and accurately placed near the lesion.

Thoma³⁶⁸ states that sometimes external irradiation combined, if possible, with intraoral therapy are employed in the initial treatment, while interstitial implants of radium form the second phase of treatment. He adds that radiation therapy is generally administered in fractional doses, and rays generated at 400 KV or higher are used externally, while those at 200 KV are used intraorally.

The limitations of conventional X-ray therapy have given rise to the use of megavoltage or super-voltage therapy. Easson⁸⁷ states that this high energy form of therapy is of special value for the radical treatment of irregularly shaped tumours for which accurate dosimetry would otherwise have been

difficult. Other advantages of the supervoltage X-rays from linear accelerators or the Theratron⁶⁰ Co unit, as listed by various authors,^{274, 341, 396} include a lessening risk of producing osteoradionecrosis of the jaws, the absence of skin erythema at the entrance point of the beam, the improvement of dose distribution throughout the tumour which results in a simplification of treatment, the volume of tissues irradiated is reduced, and a diminution of constitutional upset, because these beams are so penetrating that it is often possible to use a single portal of entry instead of two or more. The development of special wedge-shaped filter, which alter the slope of the isodose surfaces in the X-ray beam, is another significant advancement in clinical radiotherapy in the last decade.^{6, 87, 267} By suitable combinations of these beams it is possible to create sharply defined high dosage zones.

I. DIFFERENCES IN RADIOSENSITIVITY: Tumours vary in their sensitivity to radiation. The term radiosensitivity is meant to imply rapid tumour regression in response to moderate dosage, in contrast to limited or no regression even after high dosage is employed in radio-resistant tumours.²⁸⁶

According to Boyd,²⁶ the variation in sensitivity is mainly an intrinsic factor with characteristic radiosensitivity as a property of each type of tumour

cell. He adds that sensitivity remains relatively constant with each species and is linked with anaplasia. He lists the following tumours as being highly radiosensitive - the lymphosarcoma, the myeloma, the transitional cell carcinoma, and the embryonal carcinoma. The following tumour types are regarded by him as being highly radioresistant - fibrosarcoma, osteosarcoma, neurosarcoma, melanoma, glioma, and adenocarcinoma. Squamous cell carcinomas are moderately radiosensitive.

Boyd²⁶ further indicates that oxygenated cells and tissues are more sensitive to irradiation than when they are in an anoxic state, and this applies to both tumour cells and normal tissues. Novack²³¹ reports that the radiosensitivity of tumour cells can be increased by having the patient breathe in a high percentage of oxygen, thus increasing the oxygenation of the cells. Hydrogen peroxide infusions which increase the oxygenation of neoplastic cells have been reported to enhance tumour response to radiation.³⁷⁴ The same report indicates that of twenty-four patients treated by oxygenation and radiotherapy for advanced malignant disease ordinarily insensitive to radiotherapy, thirteen cases showed significant improvements.

II. EFFECTS OF IRRADIATION ON ORAL TISSUES: Radiation not only affects neoplastic lesion but normal tissues as well. Rahn and Drone²⁸⁷ state that with increased usage of high voltage irradiation in the treatment of oral malignancy, there has been a corresponding increase in the deleterious effects on normal tissue. They list some of the more common conditions encountered in patients treated by radiotherapy, and these are edema, mucositis, trismus, xerostoma, decaying teeth, and necrosis.

The effect of radiation on normal tissue surrounding the tumour is of considerable importance. According to Boyd,²⁶ there is acute inflammatory reaction followed by a subsequent thickening of the collagenous and elastic fibres with perhaps marked fibrosis. There is accompanying changes in the smaller blood vessels and lymphatics manifested by destruction of the vascular endothelium, disintegration in the muscle, and development of a proliferative endarteritis with resultant narrowing and closure of the lumen.

Osteoradionecrosis in patients treated for oral cancer using radiation therapy is of particular interest to the dentist. Rosen,²⁷⁴ James,¹⁴¹ and McLaren²²⁰ report that this complication of radiotherapy is due to radiation sclerosing vessels in the Haversian canals with consequent bone necrosis

precipitated by infection usually. The infection may be the result of dental sepsis arising from carious, badly broken-down teeth, or from an epithelitis involving the marginal gingiva.

Thoma³⁶⁸ indicates that in edentulous jaws with the mucosa intact, bone infection or sequestration are not as common as in cases where teeth are present following irradiation. On this basis he and others²⁸⁷ advocate the extraction of all teeth in the affected segment, or a complete extraction in neglected mouths prior to irradiation. Rahn and Drone²⁸⁷ indicate that extractions should be performed with the least possible trauma, thereby avoiding tissue damage that might delay the healing process prior to radiotherapy. They favour the performance of a radical alveolectomy with a good closure subsequently, since any bony protuberance may pierce the mucosa and act as a portal of entry for bacteria. Following planned extractions, the remaining teeth should be put in the best dental repair possible. Thoma³⁶⁸ recommends a course of penicillin therapy and the removal of all the teeth to be extracted in one appointment. He indicates that following extraction, a week to ten days delay is allowed before the commencement of radiotherapy.

Radiation therapy also causes a temporary suppression of salivary gland activity lasting for a

variable length of time, depending on the amount and concentration of the X-ray given. . Rahn and Drone²⁸⁷ report that xerostoma usually occurs at the end of the second week of therapy. . They advocate the use of a mouth wash to keep the oral tissue lubricated using a solution of glyceryl guaiacolate. Lochman^{169*} indicates that dryness of the mouth may continue for from nine to twelve months in patients irradiated for epidermoid carcinoma; and that full normal flow never quite returns. . On the other hand, Strickland³⁴¹ claims that the flow of saliva nearly always returns to a sufficient amount within six months of irradiation.

Frank, Herdley and Philippe¹⁰³ report that acquired dental defects are seen to develop only in those patients in whom the salivary glands have been irradiated during the treatment of oral malignancy. They state that lesions developed in the teeth of such patients irrespective of whether the teeth are inside or outside the field of irradiation, and that in patients in whom radiation doses have been administered directly to the jaws and teeth, but not to the salivary glands, such dental defects do not develop. Delclos⁸⁶ indicates that grossly the affected teeth are of the following two types:

1. Superficial caries of the neck of the tooth

which extend around the tooth and finish with an amputation at the gum line.

2. The gradual wearing away of the incisal edges or occlusal surface of the tooth with progressive reduction in height.

Frank, Herdley and Philippe,¹⁰³ and James¹⁴¹ report that loss of taste, bitterness, and difficulty in swallowing are also experienced by these patients treated with radiation therapy.

To minimize the deleterious effects on normal tissue in the course of radiotherapy, protective shields may be used to prevent the rays from affecting tissues uninvolved by the malignant growth. Thoma³⁶⁸ indicates that these shields are essentially prosthetic appliances into which is incorporated a lead sheet ($\frac{1}{8}$ th of an inch thick) cut and shaped to fit over the irradiated area.

ELECTROCOAGULATION

Meyer²²¹ states that electrosurgery has a definite place in the management of premalignant and malignant lesions of the oral cavity. This opinion is shared by Thoma³¹⁸ who lists the following indications for electrocoagulation:

1. In small malignant tumours attached to the jaw.
2. In large malignant tumours in the floor

of the mouth.

3. In malignancy of the maxilla, with or without partial invasion of the maxillary sinus.
4. In advanced cases for palliative treatment, and in patients who are debilitated, since electrocoagulation ensures a minimal loss of blood during the operation.

Meyer²²¹ differentiates three types of electrodes used in electrocoagulation of intraoral lesions - the disc electrode, the ball-point electrode, and the loop electrode. He indicates that the disc electrode technique of electrocoagulation is particularly useful in the treatment of such superficial lesions as leukoplakia and carcinoma in situ, as well as frank malignancies which are still localized. He advocates the use of the disc electrode in electrocoagulating lesions on the ventral, lateral, and dorsal surfaces of the tongue. A combination of the disc electrode and the loop electrode is useful in the electrocoagulation of tumours that are more extensive and invasive in nature. He is of the opinion that multiple primary carcinomas are frequently best treated by electrocoagulation using the disc, loop and ball-point electrodes.

The hemostasis and sealing of the lymphatics associated with electrocoagulation are added advantages

of this technique.^{221, 368}

CHEMOTHERAPY

In recent years, considerable attention and research have been directed towards the use of chemotherapy in the treatment of cancer, including oral malignancy. The desirable aim in this field is to find a chemotherapeutic agent that will suppress the division of neoplastic cells without interfering with the activity of normal cells. Karnofsky¹⁵⁸ indicates that anti-cancer drugs have produced results ranging from cure in a high percentage of cases with one type of cancer (trophoblastic choriocarcinoma) to total failures in other forms. He adds that the benefit derived from chemotherapy in head and neck cancer is irregular and uncertain at present.

Harrison and Tucker¹³³ state that chemotherapeutic success depends largely on concentrating enough of the active agent within the tumour, without producing fatal systemic side effects. They indicate that at present two main groups of cytotoxic agents are available for the treatment of head and neck malignancy, namely the alkylating agents and the antimetabolites.

Larionov¹⁷³ reports that the alkylating agents such as chloroethylamines (nitrogen mustards) and their derivatives, represent the largest group of

anti-tumour drugs at the moment, and more than thirty alkylating agents have been found to be clinically more or less effective in the treatment of various types of malignant neoplasms. He indicates that the biological action of the alkylating agents is based on their ability to combine with chemical groups of cellular components, the highly polymerized deoxyribonucleic acid being one of the most vulnerable to the action of such agents. Through a series of complicated reactions and interchange, the nucleic acid structure is disrupted, leading to a loss of cell vitality.

The best known alkylating agent is nitrogen mustard. Hanna, Gaisford and Goldwyn,¹³² and Gaisford¹¹⁴ used this drug as an adjunct in the treatment of patients with uncontrollable pain from head and neck cancer. They noted that of the patients who completed a course of infusion therapy, the majority of them experienced various degrees of relief from pain. They conclude that when ordinary sedation and narcosis no longer relieve pain, nitrogen mustard may be used.

Harrison and Tucker¹³³ indicate that the haematological toxicity of nitrogen mustard, plus its low therapeutic index and its non-selective site of activity, greatly limit the use of this agent in cancer chemotherapy. They report that other alkylating

agents such as ethoglucide and cyclophosphamide are superior in the treatment of head and neck malignancy. In their series of 80 cases of advanced head and neck cancer treated with ethoglucide and cyclophosphamide, nine patients (12 per cent.) obtained complete regression of their tumours while the majority of the patients experienced considerable relief from pain and discomfort.

Another group of well known drugs which exhibit carcinolytic and carcinostatic action are the anti-metabolites. In this group are the antifolic compounds, the purine antagonists, the pyrimidine analogues, and others. According to Lovely,¹⁷¹ methotrexate, a folic acid antagonist, is the most effective chemotherapeutic agent available at present for the treatment of oral neoplasms. He is of the opinion that this agent is the least toxic of the antimetabolites studied, and its toxicity can be further reduced by the intermittent administration of citrovorum factor 6. He indicates that methotrexate is contraindicated in patients with impaired renal or liver function, in patients who are pregnant, and it should be used cautiously in patients whose bone marrow has been damaged by infiltration of neoplastic cells, or in patients recently treated with testosterone, or in those cases treated previously by radiation therapy. In the hands of Harrison and

Tucker,¹³³ the use of methotrexate in the treatment of advanced head and neck cancer was reported to be disappointing, while Karnofsky¹⁵⁸ indicates that its usage is beneficial, securing temporary remission of the disease by 20 to 30 per cent. However, he reports that the duration of such a response rate is brief.

Others⁹¹ report favourable of the use of this agent in the treatment of oral cancer, and that the infusion of methotrexate has become a routine procedure in all patients who undergo operative procedures for intraoral malignancy at certain hospitals. The same report indicates that of 31 patients who were infused with methotrexate over a period of seven to ten days, all the patients responded favourable - tumours diminished in size, some healed and, in all patients, pain was reduced. The best results were obtained with small tumours limited to the lateral surface of the mouth and previously untreated.

A third involvement in the chemotherapy of cancer, as reported by Farber,¹⁰⁴ is the recent introduction of antibiotics to combat this disease. The antibiotics involved are actinomycin C and actinomycin D which are reported to produce striking temporary regressions in certain types of neoplastic conditions. Farber¹⁰⁴ points out that actinomycin D has a potentiating effect on radiotherapy, and a

combination of the two enhances the radiotherapeutic effect upon the skin and buccal and pharyngeal mucosa. Other antibiotics regarded by him as of chemotherapeutic value include sarcomycin and carzinophyllin.

The combined use of chemotherapy and surgery in the treatment of patients with cancer of the tongue, floor of the mouth, buccal mucosa, and tonsils, with or without clinical lymph nodes involvement, have been attempted by Golomb and Wright.¹¹¹ According to them, the rationale of such a combination is based upon the premise that perfusion with chemotherapeutic agents of the operative site, at the time of surgery, may attack any neoplastic cells left behind as well as those that might be released into the blood stream. They report that definite gross and microscopic destruction of advanced neoplasms was achieved using such a technique. Nitrogen mustard was used by Golomb and Wright¹¹¹ in the combination, while Harrison and Tucker¹³³ employed cyclophosphamide and ethoglucide in this regard.

Larionov¹⁷³ is of the opinion that chemotherapy has widened the field of cancer therapy by surgery. He predicts that the main object in cancer chemotherapy in future would be the prevention and treatment of metastasis, and this could be used preoperatively and postoperatively to check the dissemination of cancer

cells. He concludes that chemotherapy will inevitably assume an important role in the complex treatment of cancer.

Feind⁹⁸ arrives at the following conclusions after much experiences with chemotherapy in the treatment of head and neck cancer:

1. At present, the chemotherapeutic agents available have produced relief of symptoms and transient regression of tumours.
2. Only a small number of patients with arrested cases resulted from the use of chemotherapy solely.
3. Chemotherapy combined with surgery or radiotherapy help to salvage a small number of patients with very advanced inoperable cancer.
4. Isolation perfusion can give rise to hazardous complications, and control of drug toxicity to the central nervous system is unsure.
5. At present, chemotherapy should never be used to substitute surgery or radiotherapy except in very advanced inoperable cases.
6. At present, chemotherapy is a useful adjuvant to surgery and radiotherapy.
7. Caution should be exercised by teams well familiar with the handling of such drugs used in chemotherapy because of their extreme toxicity.

8. Techniques of administration have been refined, but less toxic and more cancericidal drugs need to be discovered.

THE TREATMENT OF LYMPH-NODES METASTES

The prevention and treatment of metastasis from oral cancer should be regarded equally as important as the treatment of the primary lesion. A definition of the terms used would be appropriate here. According to Martin et al.,²⁰² and Martin,²²²

- Radical Neck Dissection implies the thorough removal of the lymphatics (nodes and lymphatic vessels) from the lateral and anterior aspects of the neck that are likely to be involved by metastatic cancer.

The procedure would include the removal of the sternomastoid and omohyoid muscles, the submaxillary triangle contents, and the internal jugular vein en bloc.

- Partial Neck Dissection refers to an operative procedure which is more confined and specific in area involving the submaxillary and supraomohyoid regions.
- Bilateral Neck Dissection involves a radical neck dissection performed on both sides of the neck, usually in two stages.

- Prophylactic Neck Dissection implies that the operative procedure is intended to prevent, rather than to cure, metastatic oral malignancy. The operation is performed as a separate and independent procedure in patients with no clinically demonstrable cervical lymph node involvement when the primary lesion in the mouth is supposedly under control.

Most authorities^{71, 139, 202, 213, 220, 222, 223, 258, 267, 353, 368, 411} are of the opinion that the treatment of lymph-node metastases is a surgical problem. Martin et al.,²⁰² Copeland,⁷¹ and McLaren²²⁰ indicate that in selected cases such as when the node or group of nodes is small, radiation therapy may be used with success. Some of the criteria listed for neck dissection by proponents of this method in the management of positive lymph node involvements are:

- 1.. The primary lesion giving rise to the metastasis should be under control, or, if not controlled, there should be a plan to remove the primary at the same time when neck dissection is performed.
2. Clinically and radiographically, there should be an absence of distant metastasis.
3. Neck dissection should offer to the patient a definite better chance of cure than radiation therapy.

4. There should be no fixation of the cervical lymph nodes to underlying structures.
5. There should be no perforation of the capsule of the lymph nodes.
6. The patient should be in good general health and capable of withstanding extensive surgery.

Martin et al.,²⁰² in a review of a large series of 1,450 patients who underwent neck dissections at the Memorial Hospital, New York, report that the prognosis of cure may be influenced by the following factors:

1. Age at the time of operation - The prognosis following neck dissections appears to be rather constant through the fourth to the seventh decades of life, and dropping from about 33 per cent. to 21 per cent. in the eighth decade of life.
2. Sex - There is no differences in males and females in the prognosis for cure by neck dissection.
3. Site of the primary lesion - In cancer of the lip, the prognosis is much better than in malignancy of other intraoral sites.
4. Pathology - Adenocarcinomas secure the best cure rates for neck dissection, next is the over all group of epidermoid carcinomas, and the poorest is in metastatic melanoma.
5. Chronology of cervical metastasis - If cervical metastasis is present on admission, the five year

cure rate proves to be a little lower than if metastasis developed subsequently.

6. Number of nodes found to be involved in the surgical specimen - when one lymph node is involved the prognosis appears considerable more favourable than if multiple nodes are involved.
7. Postoperative recurrences in neck following neck dissection - In those cases in which there is no recurrences following neck dissection, the cure rate is considerably better than in cases where recurrences are seen.

Palmer and Martin,²⁵⁸ and Beahrs and Barber⁴¹ indicate that if cervical metastases are present on both sides of the neck, a bilateral neck dissection is performed, and according to the latter authors, this is best performed in stages with an interval of several weeks between dissection. However, Moore, and Frazell²²³ are of the opinion that in patients with advanced cancer, staging of the neck dissections may not be practical because of the location and extent of the primary disease. and, in such cases, simultaneous neck dissections of both sides are performed, frequently in combination with removal of the primary lesion.

Martin et al.,²⁰² in a review of 50 patients who had bilateral neck dissection, reports that 30 per cent. of patients experienced a five year cure rate.

In the series investigated by Fletcher, Braun and MacComb,⁹³ they indicate that in patients with bilateral lymph node metastases from lingual cancer and who had bilateral neck dissection, there were no survivors even after only three years. They report that, however, a significant salvage was obtained from those with lymph node metastases associated with lesions on the floor of the mouth following bilateral neck dissection.

When cervical lymph node involvements are positively identified, there is no question of a neck dissection. However, considerable controversy exists as to whether or not a prophylactic neck dissection should be done when there is no clinical evidence of lymph node involvement by oral cancer.

The proponents^{41, 85, 219, 411, 412} of prophylactic neck dissection for all cases of patients with intraoral malignancy indicate that the high incidence of lymphatic spread in this disease would justify such a procedure to be carried out at the same time when the primary lesions are under control. The percentage of cases in which cancer cells have been found to be present in cervical nodes in patients who had no clinical evidence of metastases ranges from 25 to 40 per cent. as given by advocates of prophylactic neck dissection. They also contend that there are cases in

in which the neck has to be 'opened' for adequate surgical exposure to facilitate the removal of the primary lesions and, in such cases, prophylactic neck dissection should be performed.

This view is opposed by Cade and Lee,⁶¹ Martin and his associates,^{202, 222} Copeland,⁷¹ and McLaren²²⁰ who feel that an operation of such a magnitude should only be undertaken if there is a definite indication for it. Martin et al.,^{202, 222} in an investigation of a large series of cases, report that for cancer of the tongue, for one prophylactic neck dissection that might be beneficial, four useless operations would have to be carried out. In the case of cancer of the lip, they indicate that fifteen useless operations would have been necessary in order for one to be of benefit. On this basis, they maintain that prophylactic neck dissection is not justified. They and Copeland⁷¹ share the opinion that a radical neck dissection can still be performed when the involved lymph nodes become clinically palpable.

PALLIATIVE THERAPY

There is a sizeable group of patients who present themselves with incurable cancer, either on initial consultation or due to a lack of response to therapy. Lovely¹⁷¹ claims that even with early diagnosis and treatment, 20 per cent. of all oral malignancy are incurable. He maintains that one can and

should strive to alleviate pain and prolong life even when it is impossible to effect a cure for these patients.

Meyer¹⁸³ indicates that palliative therapy is based on the premise of giving the patient the most number of comfortable days. Every effort should be made to see that the patient is as comfortable as possible.

Oral carcinomas which have progressed beyond the hope of salvage are frequently managed by radiation therapy for palliation.^{83, 219, 286} A relatively lower dosage is used, and much less complex techniques requiring less time are adequate. Palliative therapy must induce minimal reactions, for it would be poor palliation to relieve one symptom only to create new ones.

Chemotherapy in the treatment of cancer has only recently come to the fore, and various chemotherapeutic agents have been used in the palliative treatment of the incurable oral cancer patients.^{98, 274}

Moore¹⁸⁴ indicates that palliative excision of a primary tumour is sometimes justified where the growth, because of its size and smell, renders life intolerable, or when there is an immediate threat to the patient's life from haemorrhage, or when imminent death is associated with severe pain, sepsis, and cachexia.

Some authorities^{105, 183, 274} recommend the resection of the lingual nerve, or the performance of alcohol nerve blocks, and neurosurgery in the relief of pain when analgesics and narcotics are no longer of any value in controlling acute pain. They indicate that such radical procedures are only resorted to as part of the terminal care for the incurable cancer patient.

CANCER OF THE LIP

GENERAL INCIDENCE

Cross, Guralnick and Daland⁶⁵ report that of 19,664 cancer patients examined at the Pondsville Hospital during the period 1927 to 1941, there were 563 patients with cancer of the lip, representing 2.9 per cent. of all malignancies seen at that institution, while Nelson²³³ indicates that the incidence of lip cancer in Western Australia is at least 47 per year, or 94 per 1,000,000.

According to Colby, Kerr and Robinson,⁵⁰ and Sharp, Bullock and Hazlet,³²³ the lips are the most frequent site of intraoral carcinomas. Castigliano⁵¹ indicates that carcinoma of the lip consists of 31 per cent. of all oral carcinomas. While Ariel² states that one fourth to one third of oral cancers occur in the lip. On the other hand, Gardner, Schwartz and Pallen,¹¹⁹ in a review of 258 cases of oral malignancy, report that 17.8 per cent. were located on the lips. In a separate series of 167 patients with intraoral cancer, Gardner¹¹⁷ noted 33 cases occurring on the lip (18 per cent.)

SEX INCIDENCE

Cancer of the lip is a disease of men.^{26, 50, 368} According to Ariel,² 90 to 95 per cent. of patients with cancer of the lips are men. This corres-

ponds closely to the findings of Cross, Guralnick and Daland,⁶⁵ who report a 9.8 per cent. male incidence in a study of 563 patients with this disease. Similar findings are reported by Welch and Nathanson⁴⁰³ in a review of 949 cases of lower lip cancer. On the other hand, in their analysis of 41 patients with malignancy of the upper lip, they noted a 29.6 per cent. female incidence. Similar observations of a higher female incidence in upper lip cancer are reported by Sharp, Bullock and Hazlet,³²³ and Nelson.²³³

According to Bernier^{15, 16} and Bourgoyne (quoted by Gardner et al.¹¹⁹), the male to female ratio of this disease is 14:1 in favour of men, while the findings of other authorities are as shown in the following table (Table 18).

TABLE 18

CANCER OF THE LIP: SEX INCIDENCE

Author	Year	Total No. of Cases	Number of Male	Number of Female
SCHREINER and CHRISTY ³⁰²	1942	636	619	17
WIDMAN ⁴⁰⁰	1950	363	359	4
WARD and HENDRICK ⁴⁰¹	1950	259	251	8
NELSON ²³³	1955	742	699	43
SMITH ³³¹	1960	129	117	12

Ariel² indicates that in Scandinavian countries where females suffer from sideropenia (Plummer-Vinson syndrome),

cancer of the oral cavity including the lip is prevalent in women.

AGE INCIDENCE

According to Ariel² and Bernier,^{15, 16} lip cancer generally affects aged persons, usually after the fourth decade, although its occurrence in younger individuals is by no means a rarity.

Cross, Guralnick and Daland,⁶⁵ in an analysis of 563 cases, report that the age of the patients at the onset of the disease ranged from 25 to 91 years with the greatest number of cases occurring between 55 and 75 years. The mean and median age of patients in the series was 62 years. This corresponds closely to the findings of Welch and Nathanson,⁴⁰³ who report a mean age of 63.5 years for a group of 990 patients with this disease investigated by them. In a smaller series of 129 cases reviewed by Smith,³³¹ the average age for the group was 57 years.

Schreiner and Christy,³⁰² in a review of 636 cases report that the age of the patients ranged from 28 to 92 years with the greatest number occurring in the decade of 60 to 70 years, while Ward and Hendrick,⁴⁰¹ in a study of 259 cases, indicate that about 50 per cent. of the patients were over 60 years of age. Widman,⁴⁰⁰ in an investigation of 363 cases, remarks that the age incidence of patients with this disease

was equally distributed between those of 50 and 80 years of age, and that the incidence under 40 years was low.

SITE OF OCCURRENCE

The findings of several authorities^{26, 50, 51, 233, 318, 368} are that the lower lip is more frequently involved in cancer than the upper lip.

Bhaskar²⁸ and Bernier^{15, 16} claim that 95 per cent of this disease is seen on the lower lip as compared to a mere five per cent. on the upper lip. Ariel estimates the ratio of occurrence in the upper lip to the lower lip is 1:20.

Cross, Guralnick and Daland,⁶⁵ in a review of 563 patients with lip cancer, report that 497 cases occurred in the lower lip, 19 cases on the upper lip, and 47 cases on the labial commissures. They add that the left and right sides of the lip were affected with equal frequency. Similar findings by various other investigators are as shown in the following table (Table 19).

Bhaskar²⁸ and Castigliano⁵¹ indicate that the most frequent site in the lower lip afflicted by this disease is at the junction of the lateral and middle thirds, while Bernier,^{15, 16} Ariel,² and Colby, Kerr and Robinson⁵⁰, report that the vermillion border is the site of most frequent occurrence. On this issue,

TABLE 19
CANCER OF THE LIP: SITE DISTRIBUTION

Author	Year	Total No. of Cases	No. on Upper Lip	No. on Lower Lip
WELCH and NATHANSON ⁴⁰³	1937	990	41	949
SCHREINER and CHRISTY ³⁰²	1942	636	22	614
WARD and HENDRICK ⁴⁰¹	1950	259	20	239
NELSON ²³³	1955	742	50	692
SMITH ³³¹	1960	129	5	124

Atkinson et al.,⁷ in their investigation of oral cancer in Papua and New Guinea, indicate that the majority of lip cancers in New Guineans are commisural in contrast to lesions in Caucasians which usually arise on the vermillion external surface of the lip. They feel that probably it is best to regard lip lesions seen in New Guineans as extensions from lesions in the buccal mucosa of the cheek for which betel nut chewing is indicted as of etiologic significance in the development of these lesions in the buccal mucosa.

Several suggestions have been advanced in an attempt to account for the predominant occurrence of this disease on the lower lip as compared to the upper lip. Boyd²⁶ and Bernier¹⁶ indicate that the high incidence of malignancy in the lower lip may be attributed to its being slightly more protruded with

resultant greater exposure of its surface to irritating factors such as actinic rays from the sun, biting action, etc. than the upper lip which generally has a more protective posture, besides the lesser area exposed to such factors.

RACIAL DISTRIBUTION

Ariel² states that Negroes are singularly exempted from cancer of the lip although they do suffer from other forms of intraoral cancer to a degree equal with other races. . . . Similar findings of a higher occurrence of this disease in Caucasians than in Negroes are reported by Bernier,^{15, 16} Colby, Kerr and Robinson,⁵⁰ Smith,³³¹ and Cross, Guralnick and Daland.⁶⁵

ETIOLOGY

A number of factors have been evaluated as of etiologic significance in cancer of the lip.

Shafer, Hine and Levy³¹⁸ indicate that there is substantial evidence to suggest that trauma from pipe stems, plus the heat and combustion end products of tobacco, significantly contributes to the production of lip cancer. . . . This opinion is shared by Bernier,¹⁶ who indicates that despite the introduction of newer materials used in pipe-stems to reduce the traumatic effect, this is still an important etiologic factor.

Cross, Guralnick and Daland⁶⁵ report that

of 563 patients with lip cancer investigated by them, 335 were classified as tobacco users, and of these, 71 per cent. were pipe smokers, while Widman⁴⁰⁰ reports that 40 per cent. of a group of 363 patients with this disease reviewed by them were pipe smokers. On the other hand, Ariel² indicates that there is no significant data to show that tobacco causes lip cancer, and that the smoking of the hot clay pipe is probably instrumental as an etiologic factor, but it is the heat rather than the tobacco per se.

Although Wynder, Feldman and Bross,³⁹⁵ and Castigliano⁵¹ are of the opinion that syphilis is of etiologic significance in lip cancer, the findings of Cross, Guralnick and Daland⁶⁵ (7.2 per cent. of 563 patients had a positive Wasserman reaction), Widmann⁴⁰⁰ (8 per cent. of 363 cases had syphilis), and Schreiner and Christy³⁰² (3.6 per cent. of 636 cases had syphilis) are suggestive of the minor role played by syphilis in cancer of the lip. Ariel² indicates that although the relationship between syphilis and lingual cancer is probably a true one, it is doubtful whether the same relationship exists for lip cancer.

Cross, Guralnick and Daland⁶⁵ are of the opinion that trauma superimposed on a background of poor oral hygiene may be of importance as an etiological factor. This is based on their findings that

in the series of 563 patients with cancer of the lip, only 28 had fair oral hygiene and at least 69 patients gave a definite history of trauma prior to the appearance of the tumour. These included cuts while shaving, cigarette burns, injury in the course of tooth extraction, burns from sparks while engaged in welding, and repeated injuries from poorly fitting dentures and sharp jagged teeth. However, they indicate that this is not meant to imply that single trauma is a cause of carcinoma of the lip.

In the series of 259 patients with this disease reviewed by Ward and Hendrick,⁴⁰¹ they report that 26 per cent presented a history of either a single trauma or repeated trauma such as dental irritation, frequent biting of the lip, keeping tobacco on the lip, etc. On the other hand, Schreiner and Christy³⁰² indicate that trauma from razor cuts, burns, irritating teeth or dentures was a minor factor being recorded in only 58 instances in the group of 636 cases investigated by them. In the same series, they

noted that the oral hygiene of 258 patients were very poor.

Sunlight has been regarded as an important etiologic factor in cancer of the lip and the exposed skin of the body, particularly about the facial region. Boyd²⁶ indicates that the carcinogenic components of actinic rays from the sun are responsible for the high incidence of lip and skin cancer among the white population in the tropics, Australia, and the Southern United States. Cowan (quoted by Ariel²) has indicated that the high incidence of cancer of the lip in persons living in the mountainous regions of Utah is due to prolonged exposure to dry alkaline dusts and actinic rays.

This opinion is shared by Bernier,¹⁶ Ward and Hendrick,⁴⁰¹ and is substantiated by the findings of Schreiner and Christy³⁰² who report that approximately one third of the 636 patients with lip cancer

investigated by them were farmers, postmen, painters, and other out-door workers who were continually being exposed to these natural elements.

Sharp, Bullock and Hazlet³²³ are of the opinion that in dry, hot areas, where women are habitually exposed to the sun and wind without the protection from lipsticks, as in more sophisticated communities, the incidence of lip cancer in women is correspondingly higher and closely parallels the incidence of this disease in men.

Other authorities who regard actinic rays as of etiologic significance in lip cancer include Castigliano,⁵¹ Wynder, Feldman and Bross,^{394, 395} Cahn,⁴⁷ Bhaskar,²⁸ and Shafer, Hine and Levy.³¹⁸

Ariel³ indicates that in cancer of the lip, leukoplakia, keratoses, cheilitis, and fissuring are commonly noted. Ward and Hendrick,⁴⁰¹ in an analysis of 259 patients with malignancy of the lip, report that 38 per cent. of the cases had some form of precancerous conditions which included keratoses, leukoplakia, warts, papillomas, and chronic fissures, especially in the commissures. They indicate that 25 patients gave a history of having keratoses for a period of a few months to several years before the lesion became malignant, and that in the 17 patients with leukoplakia, the malignant lesion developed in the leukoplakic area.

Similar findings were reported by Cross, Guralnick and Daland⁶⁵ who indicate that 14.5 per cent. of 563 patients with lip cancer had leukoplakia and keratosis, while Smith,³³¹ in a study of 129 cases, reports that 11 per cent. of the patients had leukoplakia. On the other hand, the findings of Schreiner and Christy³⁰² tend to discount the role played by leukoplakia in lip cancer. In their study, they noted that only 2.4 per cent. of 636 patients had leukoplakia.

The relationship between cancer of the lip and certain occupational factors was reported by Boyd,²⁶ who states that malignancy of the lip was especially common among fishermen on the west coast of Scotland, who, in mending their nets, held the bone needle threaded with tarred twine between their lips. Similarly, Professor Schuchardt⁵⁵ indicates that many of the painters of luminous dials for watches and clocks developed carcinomas of the lip as a result of using their lips to point the brushes without realising the danger of the radioactive fluorescent substances.

CLINICAL FEATURES

According to Shafer, Hine and Levy,³¹⁸ the clinical appearance of carcinoma of the lip varies considerably, depending mainly on the duration of the lesion and the nature of the growth. They indicate that frequently the lesion begins as a small area of

thickening, followed by induration with ulceration to progress to an exophytic growth or a crater-like defect with an irregular surface.

Smith³³¹ indicates that the initial lesion may resemble a blister, scale or crust, which usually develops into one of the three common growth patterns - exophytic, ulcerating and verrucous. He adds that the exophytic growth frequently involves a large part of the lip with thickening and induration, whereas the ulcerating type begins as an ulcer or fissure with peripheral induration; the verrucous lesion presents an irregular surface with fissures and ulceration.

In recording the size of the primary lesion on the lip, Ward and Hendrick⁴⁰¹ report that of 250 cases, 26 per cent. had lesions under 1 cm. in diameter, 32.7 per cent. had lesions between 1 and 2 cm. in diameter, 18 per cent. had lesions between 2 and 3 cm. in diameter, while 16 per cent. had lesions over 3 cm. in diameter. They add that in some cases the primary lesions involved either one -half or the entire lip, while others extended to involve the cheek.

In the 563 patients with this disease investigated by Cross, Guralnick and Daland,⁶⁵ the size of the primary lesion was recorded in 349 cases with the great majority having a maximum diameter of 2 cm. or less (76.5 per cent.) In 39.2 per cent. of the cases, the

primary lesions measured 1 cm. or less in diameter, while the majority of the remainder had a range of from 2.1 to 5.0 cm. in diameter. They report that a small number of extensive growths measured from 5.1 cm. to as much as 12 cm.

HISTOPATHOLOGIC TYPES

Smith³³¹ states that the great majority of malignant neoplasms of the lip are epidermoid carcinomas exhibiting various stages of tissue changes. In the series of 129 cases investigated by him, there were 122 epidermoid carcinomas, six basal cell carcinomas, and one tumour of reticuloendothelial origin.

Ariel² indicates that most lip cancers are squamous cell carcinomas and are frequently of low-grade malignancy (Grades I and II), and this is especially true in primary lesions which have not been treated previously. They are of the opinion that lip cancers that have been treated previously tend to fall into Grades III and IV, for incomplete efforts of cure appear to increase the degree of anaplasia. In the series of 259 cases reviewed by Ward and Hendrick,⁴⁰¹ they report that all were squamous cell carcinomas varying from well-differentiated Grade I to highly anaplastic Grade IV (Broder's classification). They indicate that most of the lesions were of low-grade activity with 84 per cent. either in Grade I or Grade II.

Widman,⁴⁰⁰ in an analysis of the histopathology of 259 cases, presents the following distribution of graded lesions:

Grade 1	119 cases	46%
Grade 2	51 cases	20%
Grade 3	25 cases	10%
Grade 4	3 cases	1%
Not graded	61 cases	23%

Gardner, Schwartz and Pallen¹¹⁹ indicate that carcinoma of the upper lip grows more rapidly than carcinoma of the lower lip. This opinion is shared by Ariel² who states that cancer of the upper are usually more malignant than those of the lower lip and tend to fall into Broders' Grades II and III.

METASTASES

Shafer, Hine and Levy,³¹⁸ Ariel,² Boyd,²⁶ and Colby, Kerr and Robinson⁵⁰ state that carcinoma of the lip is generally slow to metastasize, while Thoma³⁶⁸ claims that the development of metastases occur early in the course of the disease.

In a review of 563 cases, Cross, Guralnick and Daland⁶⁵ observed that 113 patients had metastatic regional lymph nodes involvement, while Ward and Hendrick,⁴⁰¹ in an analysis of 259 cases, report that 119 patients had palpable nodes. Ariel² states that about 10 per cent of all patients with cancer of the

lip develop metastases to the regional lymph nodes.

The incidence of metastases in the series of 179 patients with lip cancer investigated by Modlin²¹³ is as follows (Table 20).

TABLE 20

INCIDENCE OF METASTASES IN LIP CANCER

Metastases	Number of Patients	Percentage
No metastases on admission	158	88.8
Metastases on admission	21	11.7
Metastases during follow-up	15	9.6
Total Metastases (5 year follow up)	36	20.0
	179	100.0

Source: MODLIN²¹³

As can be seen from the table, the total incidence of metastases was 20 per cent. of 179 patients, but only 9.6 per cent. of the patients admitted without evidence of metastasis subsequently developed positive nodes.

Cancer of the lower lip usually metastasize to the submental and submaxillary lymph nodes, while the most frequent sites for metastases from cancer of the upper lip are to the preauricular and infraparotid lymph nodes.^{2, 15, 50, 318} Thoma³⁶⁸ claims that involvement of the cervical nodes are unusual, and the

supraclavicular and axillary involvement is very rare, while bilateral metastases are common. Shafer, Hine and Levy³¹⁸ state that when metastasis occurs, it is usually ipsilateral, but contralateral metastasis may occur, especially if the lesion is near the midline of the lip where there is a cross drainage of the lymphatics. Ariel² indicates that there is a rather high incidence of crossed metastasis, because of the abundance of cross anastomoses in the lymphatic drainage in the mid-line of the lip.

According to Boyd²⁶ and Bernier,¹⁵ metastasis occurs mainly via the lymphatics and seldom by the blood stream. Widman⁴⁰⁰ claims that lesions involving the buccal commissures and buccal mucosa metastasize earlier and more frequently, while Ariel² indicates that upper lip cancers show a greater tendency to metastasize to regional lymph nodes.

Ariel² states that the observation that approximately 20 per cent. of the patients present themselves after metastases have occurred show the extensive delays in these cases. Smith,³³¹ in a review of 129 cases, reports that the delay time from the onset of the disease to when treatment was instituted was about 19 months.

TREATMENT

The surgical accessibility and the radio-

sensitivity of lip cancers have caused surgeons and radiologists to compete for their care. Shafer, Hine and Levy,³¹⁸ Boyd,²⁶ and Ariel² are of the opinion that in skilled hands, surgery and X-ray irradiation give comparable results. This view is shared by Schreiner and Christy,³⁰² but they indicate that the cosmetic results following irradiation are superior to those with surgery.

Bernier¹⁵ is of the opinion that surgical excision is the best form of therapy for carcinomas of the lip. Others who place greater emphasis in surgery as the treatment of choice include Ward and Hendrick,⁴⁰¹ Thoma,³⁶⁸ and Cross, Guralnick and Daland.⁶⁵

Thoma³⁶⁸ indicates that for small superficial growths, the entire lesion can be removed as a biopsy procedure by a V excision, whereas larger and deeper lesions should be excised completely to include the entire growth with a safe margin of normal tissue. He adds that electrocoagulation may be used in advanced cases and in recurrent growths previously treated with irradiation.

More specifically, Ward and Hendrick⁴⁰¹ state that lesions either on the lower or upper lip, or on the commissures which are under 1.5 cm. or 2 cm. in diameter and do not infiltrate deeper than 1 cm. or 1.5 cm. can be well controlled by the V-shaped excision,

care being taken to extend the incision well around the growth, that is, 1 cm. on each side. Cross, Guralnick and Daland⁶⁵ point out that this can be performed under local anesthesia, while the surgical treatment of larger lesions involve a more extensive quadrilateral excision with some type of plastic reconstruction of the lip. Ward and Hendrick⁴⁰¹ indicate that electrosurgery may be used in cancers involving the entire lower lip to the mandible.

On the other extreme, Widman⁴⁰⁰ states that cancer of the lip should be considered a radiologic problem. He indicates that patients with this disease in reasonably early stages, and in the absence of lymph nodes involvement have been successfully treated by various forms of radiotherapy. He adds that even in advanced, bulky, infiltrating lesions without lymph node metastasis, there is a good chance of permanent cure using irradiation. Nelson,²³³ in reviewing a large series of cases treated mainly by radiological techniques, reports that the use of radium in the treatment of this disease is satisfactory. He indicates that perhaps better results can be attained if surgery is used more vigorously as a supplementary method of treatment in uncontrolled primary growths, and when the presence of secondary glands is unquestionable.

Ariel² indicates that a number of factors influence the selection of the various methods employed in the treatment of patients with cancer of the lip. He divides these factors arbitrarily into three general groups:

1. CHARACTERISTICS OF THE NEOPLASM, which include the size and location of the tumour, its growth characteristics, and its microscopic grading. Thus, he indicates that small tumours of 1 and 2 cm. in diameter and which do not infiltrate deeply can be treated satisfactorily with either surgical excision or irradiation, while extensive superficial growths involving a large part of the lip are best irradiated. On the other hand, surgical excision is generally preferred to irradiation in large neoplasms.

Considering the growth characteristics of the tumour, he prefers to irradiate lesions that have a tendency to spread superficially, whereas in exophytic tumours and those that infiltrate the lip extensively to involve the mandible, surgical resection is the method of choice.

For tumours involving the commissures, Ariel² advocates X-ray irradiation followed by surgical resection, or surgical resection alone as the treatment of choice, for according to him, irradiation

tion alone seldom cures these neoplasms. He is of the opinion that well-differentiated Grade I cancers are best removed surgically, whereas radiotherapy is preferred in highly anaplastic Brokers' Grade IV tumours. He indicates that if metastases to the cervical lymph nodes are present, local excision of the lesion plus neck dissection is the method of choice unless contraindications exist.

2. CHARACTERISTICS OF THE PATIENT, the most important being the age of the patient. In his opinion, irradiation should be avoided, if possible, in the treatment of this disease in young patients, because of the undesirable cosmetic effects due to the development of late radiation reactions, and also because of the possibility of producing a late radiation cancer.
3. CLINICAL STATUS OF THE PATIENT, which includes whether or not the patient has received previous therapy, and the duration of the cancer. A cancer recurring after irradiation would preferably be treated by surgical resection and vice versa. As for duration of the cancer, Ariel² indicates that a lesion of long duration that is still small in size and without metastasis would imply a tumour of low grade malignancy and would be suitable for surgical excision.

Ariel² indicates that in the surgical treatment of primary lesions, the surgical procedures vary from a simple local excision in small well differentiated growths to resection of the entire lip with a wide margin of intervening tissue and perhaps a partial mandibulectomy, while in radiation therapy in the treatment of this disease, practically every form of X-ray therapy has been used from low voltage contact therapy to supervoltage X-ray radiation. He points out that various radioactive isotopic techniques are gradually replacing radium. Thus, radioactive cobalt, caesium, iridium, gold, and tantalum are being used.

In the treatment of positive lymph node metastases in lip cancer, surgery is generally accepted as the method of choice.^{2, 233, 302, 368, 400} However, prophylactic neck dissections in patients with this disease are unjustified and unwarranted.^{2, 213, 233}

PROGNOSIS

Despite the fact that cancer of the lip is perhaps the most common form of intraoral malignancy, it accounts for relatively few deaths as compared with other oral cancers, implying a comparatively favourable prognosis.

Ward and Hendrick,⁴⁰¹ in their review of 259 patients with this disease, present the following table showing the end results of the different methods of treatment employed (Table 21).

TABLE 21

END RESULTS IN ALL PATIENTS TREATED FOR LIP CANCER

		Three Year Cures (per cent.)	Five Year Cures (per cent.)
PRIMARY GROUP	180	76	72.1
SURGERY	72	93	89
IRRADIATION	69	81	79
COMBINED	39	58	51
SECONDARY GROUP			
ALL METHODS	79	66	64
TOTAL NUMBER	259	74.9	70.1

SOURCE: WARD & HENDRICK⁴⁰¹

As can be seen from the table, the overall five year non recurrence rate for the entire group was 70.1 per cent.

Widman,⁴⁰⁰ in an analysis of 259 cases treated exclusively by various radiological techniques, reports a cure rate of 83 per cent., while a much lower absolute cure rate of 58.9 per cent. was obtained by Schreiner and Christy³⁰² who treated 636 cases mainly by X-rays and radium.

Cross, Guralnick and Daland⁶⁵ report that the total cure rate for 491 patients with proven carcinomas of the lip, irrespective of the methods of treatment,

was 67.1 per cent. based on the three year cures, and 63.6 per cent. when based on the five year cures. They indicate that lesions of the labial commissures were approximately twice as difficult to control as those located in other parts of the lips.

In an investigation of the life expectancy of 990 cases of lip cancer, Welch and Nathanson⁴⁰³ report that of 20 untreated cases in the series, 50 per cent. of the patients were dead in 19 months, 75 per cent. in 31 months, and five years from the onset of the disease, 93 per cent. were dead, whereas by the seventh year, all the patients were dead. They indicate that of 929 treated patients with cancer of the lower lip, 50 per cent. were dead in 5.5 years and 75 per cent. were dead in 10.5 years. Five years after the onset of the disease, 52.5 per cent. of the patients were dead, and at ten years, 73.5 per cent. were dead. On the other hand, of 41 treated patients with malignancy of the upper lip, 50 per cent. were dead in 3.5 years after the onset of the disease, while five years after the onset of the disease, 58 per cent. were dead, and at nine years, 66 per cent. were dead.

According to Bernier,¹⁵ Boyd,²⁶ and Colby, Kerr and Robinson,⁵⁰ the general prognosis of patients with lip cancer is regarded as good. This opinion is shared by Kremer and Arhelger¹⁵² who feel that the excellent

prognosis of patients with early lip cancer has been employed to induce complacency and procrastination, or to permit the use of less than adequate methods of therapy.

FACTORS INFLUENCING PROGNOSIS

The prognosis of patients with lip cancer is influenced by a number of factors which include size and site of the primary lesions, the presence of metastases, the method of treatment, previous treatment received, and the pathological grade of the primary tumours.

I. SIZE OF THE PRIMARY LESION:

Ariel,² Shafer, Hine and Levy³¹⁸ and Cross, Guralnick and Daland⁶⁵ indicate that the size of the primary lesion influences the end results of treatment. This is substantiated by the findings of Ward and Hendrick⁴⁰¹ who report the influence of this factor on the cure rate as follows: in 74 patients who had lesions under 1 cm. in diameter, the cure rate was 95 per cent.; in 60 patients with growths of between 1 and 2 cm. in diameter, the cure rate was 80 per cent.; in 27 patients with tumours measuring between 2 and 3 cm., the cure rate was 59 per cent., and for those with lesions of over 3 cm. in diameter (19 patients), the five year cure rate dropped to 41 per cent.

II. SITE OF THE PRIMARY LESION:

Ariel² states that carcinomas of the upper lip are usually more malignant than those of the lower lip and tend to fall into Broders' Grades II and III with a greater tendency to metastasize. Cross, Guralnick and Daland⁶⁵ have reported that carcinomas of the labial commissures were approximately twice as difficult to control as those located in other parts of the lip, based on their treatment of 491 recorded patients with lip cancer.

III. METASTASES

According to Shafer, Hine and Levy³¹⁸ and Ariel,² the presence of metastases to the lymph nodes markedly influences the prognosis. Cross, Guralnick and Daland⁶⁵ report that of 39 patients in their series who underwent neck dissection with pathologically proved cervical lymph node metastases, only 35.9 per cent. attained the three year cure rate as compared to 67.1 per cent. of three year cures for the entire group of 491 patients. Similarly, Widman⁴⁰⁰ reports that of 27 patients treated for positively proved metastatic lesions, only 7.4 per cent. survived five years or more as compared to a cure rate of 83 per cent. for the entire series of 259 cases.

IV. METHOD OF TREATMENT AND TREATMENT RECEIVED PREVIOUSLY

Ward and Hendrick,⁴⁰¹ in an analysis of 259 patients with this disease, treated 79 patients

exclusively with surgery in which a five year non recurrence rate of 89 per cent. was obtained. In another group of 69 patients, irradiation was employed exclusively in which there was a five year non recurrence rate of 79 per cent. On the basis of these data, they conclude that surgery gives between 10 to 12 per cent. better five year non recurrence rate than radiotherapy. However, Ariel² indicates that it is difficult, if not impossible, to compare the end results of the different therapeutic methods in curing lip cancer, because of the many variable factors present in the groups of patients. He adds that both surgical and radiologic methods, properly applied, will cure almost 100 per cent. of small early lip cancers.

With regards to previous treatment, he states that all reporting authors indicate a marked decrease in curability of recurrent lesions. Cross, Guralnick and Daland⁶⁵ report that a five year cure rate of 50 per cent. was obtained for the group of 43 patients with recurrent lip cancer in contrast to 63.6 per cent. of five year cures for primary treated tumours.

V. PATHOLOGICAL GRADE OF PRIMARY TUMOURS:

Shafer, Hine and Levy,³¹⁸ and Cross, Guralnick and Daland⁶⁵ indicate that the histologic grade of the lesions influence the prognosis, those with a lower grade of malignancy having a better prognosis.

CANCER OF THE TONGUE

GENERAL INCIDENCE

Martin, Munster and Sugarbaker²⁰¹ state that cancer of the tongue comprises about 25 per cent. of all intraoral tumours, and represents approximately two to three per cent. of all human cancer at the Memorial Hospital, New York.

In an analysis of the record of the Tata Memorial Hospital in Bombay, India, Paymaster and Shroff²⁴⁴ report that there were 30,000 patients with carcinomas from the period 1941 to 1955 and, of these, there were 4,200 patients with lingual carcinoma representing 12 per cent. of the total carcinoma cases seen at that institution.

Marcial¹⁷⁹ indicates that in Puerto Rico, carcinoma of the base of the tongue is the most frequent form of intraoral and pharyngeal cancer, and represents about 2.2. per cent. of all forms of cancer.

On the other hand, Rahausen and Sayago²⁸¹ remark that carcinoma of the tongue is not a frequent disease. They report that of 10,000 cancer patients seen at the Radium Institute in Santiago, Chile, over a period of 14 years, only one per cent. of the whole group was diagnosed as lingual cancer.

Windeyer,⁴⁰⁸ in an analysis of 279 patients with cancer of the tongue over a period of twelve

years, indicate that it represents less than two per cent. of the total cases of cancer registered in the Middlesex Hospital in London.

According to Nelson,²³³ the number of patients with cancer of the tongue seen over a period of twenty years at the radium department of the Royal Perth Hospital in Perth was 139, giving an average of seven cases per year. He indicates that this is a higher incidence than that of cancer of the other parts of the oral cavity seen over the same period.

Dargent, Mayer and Bertoin,⁸⁰ in a study of 580 cases of malignant tumours of the tongue, indicate that there is a decrease in the incidence of this disease in France, and ascribe this to a decrease in the prevalence of syphilis, an improvement in the care for general and dental health, and a decrease in acute or chronic alcoholism.

Ariel³ points out that of the 4,890 deaths from cancer of the buccal cavity and pharynx in the United States in 1951, there were 1,177 deaths from lingual cancer, representing 0.5 per cent. of all cancer deaths and 0.8 per cent. per 100,000 population. He presents the following table which shows the incidence of this disease (Table 22).

TABLE 22
INCIDENCE OF LINGUAL CANCER

A. Incidence per 100,000 Population			
Author	Year	Location	Incidence
NYSTROM	1922	Sweden	1 per 100,000
LEVIN	1944	New York State	3 per 100,000
TOD	1948	England	3 per 100,000
JACOBSSON	1948	Sweden (Radium-hemmet)	1/2 per 100,000
B. Incidence of Lingual Cancer (Per cent. of all cancers)			
Author	Year	Location	Per cent.
NYSTROM	1911-12	Sweden	0.9 of 6,517 cancers
PACK and LEFEVRE	1917-29	New York City (Memorial Hosp.)	4.8 of 16,565 "
HARNETT	1938-39	England	1.9 cancers
KHANOLKAR	1941-43	India	1.8 of 2,880 cancers
JACOBSSON	1931-42	Sweden (Radium-hemmet)	1.8 of 15,388 "
GIBBEL, CROSS and ARIEL	1936-46	Hines, Illinois	1.8 of 17,327 "

Source: ARIEL³

According to Bernier¹⁶ and Tiecke,³⁶¹ over half of all intraoral carcinomas occur in the tongue, thus making this region of the oral cavity the most frequent site of mouth cancer. Although Gardner, Shwartz and

Pällen¹¹⁹ indicate that in their studies the tongue was the most common location of oral carcinoma, only 27.5 per cent. of the patients had lesions in this intraoral site out of a total of 258 cases of oral cancer patients investigated. In a separate series of 167 cases of intraoral malignancy reviewed by Gardner,¹¹⁷ he observed that 28 per cent. were located on the tongue. On the other hand, Ueno et al.,³⁷³ in an analysis of 770 cases of oral cancer, report that the tongue was involved in only about 14 per cent. of cases.

Colby, Kerr and Robinson⁵⁰ claim that carcinoma of the tongue is the second most frequent form of oral cancer. This view is shared by Castigliano⁵¹ who states that cancer of the tongue accounts for 24.5 per cent. of all oral cancer. On the other hand, Shafer, Hine and Levy³¹⁸ are of the opinion that the incidence of cancer of the tongue varies from 25 per cent. to 50 per cent. of all oral carcinomas.

SEX INCIDENCE

Shafer, Hine and Levy³¹⁸ state that cancer of the tongue is relatively uncommon in women, except in certain parts of the world, especially the Scandinavian countries, where the incidence of all intraoral carcinoma in women is high because of the common occurrence of Plummer-Vinson syndrome. Ariel,³ in an extensive review of the literature, presents the following

table showing the sex incidence of this disease (Table 23).

TABLE 23

PERCENTAGE OF WOMEN WITH CANCER OF THE TONGUE
(Report from different geographic locations)

Author	Year of Report	No. of Cases	% of Women	Location
EHRlich	1909	64	2	Austria
RICHARDS	1942	167	20	Canada
VIDEBACK	1945	---	37	Denmark
HARNETT	1947	287	14	England
MUSTAKALLIO	1948	202	49	Finland
SEBILEAU	1930	---	5	France
PETERS	1920	48	17	Germany
KHANOLKAR	1944	522	8	India
SIMEONI	1934	---	10	Italy
WASSINK	1935	---	15	The Netherlands
WEYDE	1947	---	36	Norway
PETROFF	1935	192	33	Russia
NYSTROM	1922	159	47	Sweden
JACOBSSON	1948	277	45	Sweden
SCHINTZ and ZUPPINGER	1937	203	7	Switzerland
MARTIN, MUNSTER and SUGARBAKER	1940	556	13	United States

Source: ARIEL³

From the author's own review of the literature, the following table has been prepared showing the sex incidence of this disease (Table 24).

TABLE 24
CANCER OF THE TONGUE: SEX INCIDENCE

Author	Year of Report	Total No. of Cases	% of Women	% of Men
WELCH and NATHANSON ⁴⁰³	1937	835	7.4	92.6
MARTIN, MUNSTER and SUGARBAKER ²⁰¹	1940	556	13	87
LYALL and SCHETLIN ¹⁷²	1952	76	28.9	71.1
RAHAUSEN and SAYAGO ²⁸¹	1954	113	13.2	86.8
ASH and MILLAR ¹⁰	1955	441	24.7	75.3
TIECKE ³⁶¹	1957	---	14.1	85.9
CADE and LEE ⁶¹	1957	653	22	78
PAYMASTER and SHROFF ²⁴⁴	1958	700	20	80
TRIEGER et al. ³⁶⁵	1958	198	15.6	84.4
STEPANOV ³³⁵	1960	216	33.3	66.7
FLAMANT et al. ⁹⁵	1964	904	13	87
UENO et al. ³⁷³	1964	109	34.9	65.1

Cade and Lee⁶¹ indicate that the sex incidence of this disease has altered significantly throughout the years. They report that whereas in 1925 ten male cases were encountered for each female case, this ratio has fallen to 2:1 in the period 1951-1955. This observation

is based on their analysis of cases seen at the Westminster Hospital in London:

CHANGING RATIO OF MALE TO FEMALE CASES

1925-29	10:1
1930-34	5:1
1935-39	4.5:1
(WAR YEARS EXCLUDED)	
1946-50	2+:1
1951-55	2+:1

AGE INCIDENCE

Shafer, Hine and Levy³¹⁸ state that cancer of the tongue is essentially a disease of the elderly, but it may occur in relatively young persons.

Martin, Munster and Sugarbaker,²⁰¹ in an analysis of 556 cases, report that the average age of the patients with this disease was 58 years, with the oldest patient being 89 years old and the youngest 17 years of age. This corresponds closely to the average age of 59 years for the group of 904 patients reported by Flamant et al.⁹⁵ In this series the largest number of patients was seen in the 55 year age group.

In a series of 700 cases studied by Paymaster and Shroff,²⁴⁴ they observed that the highest incidence was in the age group of 40 to 45 years, while Rahaussen and Sayago,²⁸¹ in a review of 113 cases, indicate that

the largest number of patients belonged to the decade between 50-59 years of age. The findings of the later investigators coincide with those of Voutilainen and Tuovinen,³⁸¹ who report that most of the patients (out of 137 cases) with this disease were in the age group between 50-60 years.

Stepanov,³³⁵ in an investigation of 216 cases, indicates that 17.6 per cent. of the patients were under 40 years of age, with 4.6 per cent. under 30 years old. On the other hand, Ariel³ claims that less than three per cent. of patients with lingual cancer are under 40 years of age. He and Tiecke³⁶¹ state that the average age of patients with this disease is about 55 years old. This closely parallels the average age of 53 years reported by Bernier¹⁴ for patients with malignancy in this region of the oral cavity. He indicates that this is somewhat lower than the average age of patients with cancer of the cheek, the palate or the gingival mucosa. Ash and Millar,¹⁰ in a review of 441 cases, report an average age of 63.2 years.

In a study of the median age of 835 patients with this disease, Welch and Nathanson⁴⁰³ indicate this was 61 years, while Ueno et al.³⁷³ give the mean age of 53.1 years in a group of 103 patients investigated by them.

SITE OF OCCURRENCE

Shafer, Hine and Levy³¹⁸ state that the specific site of development of cancer of the tongue is of great significance, since those tumours on the posterior portion of the tongue are usually of a higher grade of malignancy, metastasize earlier, and offer a poorer prognosis.

Tiecke³⁶¹ claims that the majority of lingual cancer are located at the posterior portion and base of the tongue. This is supported by the findings of Paymaster and Shroff,²⁴⁴ who, in a review of 700 cases, report that 530 patients had lesions at the base of the tongue and 180 had growths located on the anterior portion. Marcial,¹⁷⁹ in a study of 439 cases, indicates that slightly more than 50 per cent. were located at the base of the tongue.

On the other hand, Frazell and Lucas,⁹⁶ in a review of 1,554 cases, report that 65 per cent. of the lesions were seen on the anterior two-thirds of the tongue, and only 26 per cent. at the posterior one-third. The findings of Baud³⁴ also show a higher incidence of anterior two-thirds lesions than posterior one-third lesions. In a review of 1,055 cases, she noted that 724 patients had lesions involving the anterior two-thirds of the tongue as compared to 331 who had their growths on the posterior one-third of this organ. Similarly, Flamant et al.,⁹⁵ in an analysis of 904 patients with this disease, report that 513 cases were

found on the mobile anterior portion of the tongue, and 368 cases were located at the base of the tongue. The findings of Windeyer⁴⁰⁸ in 243 cases were 144 cases involving the anterior two-thirds of the tongue, 83 involving the posterior third, and 14 involving the whole of this organ.

Regarding a further subdivision of the site distribution of this disease, Shafer, Hine and Levy,³¹⁸ and Colby, Kerr and Robinson⁵⁰ state that the most frequent sites of lingual carcinoma are the lateral borders and ventral surface of the tongue, and that it is relatively rare on the tip and dorsum of this organ except in those cases which are associated with syphilitic glossitis. This view is shared by Rahausen and Sayago,²⁸¹ and Bernier.¹⁶ It is supported by the findings of Flamant et al.,⁹⁵ who report that of 513 anterior lesions, 396 were located on the lateral borders, 64 on the ventral surface, 37 on the dorsal surface and 16 at the tip of the tongue. They indicate that there was a significantly higher incidence of tumours on the left than on the right side of the tongue.

The findings of Ariel³ were 60 to 70 per cent. of such lesions occurring along the lateral borders of the tongue, 10 to 15 per cent. on the dorsum, 10 to 25 per cent. on the base, and 5 to 15 per cent. on the

ventral surface. Martin, Munster and Sugarbaker,²⁰¹ in a study of 556 cases, noted that about 50 per cent. were located along the edge of the tongue. They and Ariel³ indicate that cancer of the tongue usually does not occur on the dorsum just anterior to the lingual V.

ETIOLOGY

A definite relation appears to exist between cancer of the tongue and certain disorders. Among these is syphilis, which has been evaluated as of considerable etiologic significance in lingual malignancy.

Ariel³ believes that there is a significant relationship between the presence of syphilis and the incidence of cancer of the tongue. He presents the following table showing the importance of this relationship (Table 25). Similarly, Trieger and his co-workers³⁶⁵ regard syphilis as an important precursor to lingual cancer. They indicate that this relationship is only significant with cancer of the anterior two-thirds of the tongue and not the posterior third. Of 108 patients investigated by them, they report that 20 (18.5 per cent.) had a positive history, positive findings, or positive serology for syphilis.

TABLE 25

INCIDENCE OF SYPHILIS IN TONGUE CANCER

Author	Year of Report	No. of Cases of Lingual Cancer	% of cases with history of syphilis or positive Wasserman reaction or both on admission
CARY	1920	199	14
SCHREINER and BROWN	1926	127	48
LUND	1933	401	17
MARTIN, MUNSTER, and SUGARBAKER	1940	556	33
LEVIN, KRESS, and GOLDSTEIN	1942	146	14
SHARP and SPICKERMAN	1947	83	13
JACOBSSON	1948	277	14
GIBBEL, CROSS, and ARIEL	1949	230	22

Source: ARIEL³

Wynder, Feldman and Bross,³⁹⁵ in an investigation of 175 patients with cancer of the tongue, report that among 86 patients with malignancy of the anterior two-thirds of the tongue, 19 (22 per cent.) had a history of syphilis, whereas among 89 patients with cancer involving the posterior one-third of the tongue, only three per cent. had a history of syphilis. They indicate that although there appears to be a high correlation between syphilis and

cancer of the anterior two-thirds of the tongue, the possibility of the carcinogenic effect arising from the once popular arsenic therapy, which was the treatment of choice of these cases before the advent of anti-biotics, cannot be dismissed casually.

Martin¹⁸⁰ indicates that in otherwise healthy men in the 55 to 60 year old age group, the general incidence of syphilis is between four to six per cent., while more than 30 per cent. of the men in this age group with cancer of the tongue will be found to have syphilis. He and his colleagues²⁰¹ and Shafer, Hine and Levy³¹⁸ are of the opinion that the relationship between syphilis and lingual cancer is purely from a local effect of syphilis rather than a generalised or systemic effect. Bernier¹⁶ shares this view, but indicates that it is unlikely that patients with syphilis have a predisposition for cancer in this part of the oral cavity.

Although Rahausen and Sayago²⁸¹ noted that 30 per cent. of the 113 patients with lingual malignancy investigated by them gave a positive serologic reaction for syphilis, they can see no basis for believing that syphilis is a real causative factor. Similarly, Paymaster and Shroff²⁴⁴ feel that syphilis has been overemphasized as a predisposing factor in cancer of the tongue, although they indicate that 10 per cent.

of 700 patients with lingual malignancy investigated by them had evidence of a positive serologic test for syphilis.

Dargent and Bertoin,⁸⁰ in a review of 580 cases of lingual cancer, claim that constant irritation from spicules, untreated carious teeth, and poor fitting dental restorations played an important role in the production of tongue cancer, while Paymaster and Shroff²⁴⁴ report that poor oral hygiene and dental caries were associated with carcinoma of the tongue in almost 70 per cent. of a series of 700 patients with lingual malignancy studied by them. Similarly, Rahaussen and Sayago²⁸¹ are of the opinion that mechanical irritation against a sharp tooth is an important etiologic factor in this disease. They indicate that of the 113 cases of lingual cancer reviewed by them, 22 cases were associated with mechanical trauma against a sharp tooth.

On the other hand, Ariel³ indicates that oral sepsis and/or dental sepsis as etiologic factors in the production of cancer of the tongue are difficult to evaluate. He states that no definite inference can be made between such factors and lingual malignancy, although oral hygiene is extremely poor in about one third of the patients with cancer of the tongue. However, commenting on the relationship of

trauma and lingual cancer, he states that in 5 to 20 per cent. of patients with cancer of the tongue, the lesions are situated at a site in juxtaposition to a malfitting denture or a carious tooth.

Shafer, Hine and Levy³¹⁸ indicate that leukoplakia is a common lesion of the tongue which has been observed many times to be associated with tongue cancer. Bourgoyne (quoted by Gardner, Shwartz and Pallen¹¹⁹) states that lingual carcinoma is commonly preceded by leukoplakia, while Sarnat and Schour³⁰¹ mention a case reported in which an initial diagnosis of leukoplakia of the tongue was made from biopsy, and eighteen months later, biopsy indicated carcinoma.

Ariel³ indicates that leukoplakia is reported in 10 to 40 per cent. of patients with lingual cancer, and that in several instances, carcinomatous lesions are noted upon leukoplakia plaques on the tongue. Trieger and associates³⁶⁵ report that of 108 patients with cancer of the tongue investigated by them, 14.8 per cent. had leukoplakia co-existing with the carcinoma. A slightly lower incidence of 11 per cent. of leukoplakia was observed by Rahausen and Sayago²⁸¹ in 113 patients with tongue cancer. However, they believe that leukoplakia is an important local factor in lingual cancer, and that in their series, this diagnosis had been omitted in several cases because

the tumour itself had destroyed the pre-existing leukoplakia. Paymaster and Shroff,²⁴⁴ in an analysis of 700 patients, report that leukoplakia co-existed with carcinoma in 32 per cent. of cases.

Shafer, Hine and Levy³¹⁸ indicate that other factors which have been thought to contribute to the development of carcinoma of the tongue are alcohol and tobacco. However, it is difficult to draw any conclusions about a possible cause and effect relationship because of the prevalent use of these substances. The additional factor of malnutrition in those individuals who consume large quantities of alcohol is too great to warrant the hypothesis that the use of alcohol per se is of etiologic significance.³

SIGNS AND SYMPTOMS

According to Ariel,³ the initial symptom of cancer of the tongue is usually the presence of a painless mass or ulcer (40 per cent.) A painful mass or ulcer is noted in about one fourth of the patients, sore throat and dysphagia are present in 10 per cent. of the patients, and in 4.5 per cent., a mass in the cervical region was the initial presenting complaint.

In the series investigated by Martin, Munster and Sugarbaker,²⁰¹ in over 50 per cent. of cases there was no complaint of pain, except of the physical presence of the lesions. They indicate that the

posterior third or base of the tongue has little or no tactile sense, and since lesions situated in this region cannot be visualized by the patient, such growths are therefore apt to reach a larger size or even to metastasize before producing symptoms sufficient to induce the patient to seek treatment.

Ueno et al.,³⁷³ in recording the initial complaints of 106 patients with lingual cancer, report that 51 patients complained of local pain, and 39 of the presence of a mass on the tongue. In addition, 14 patients complained of some extraoral symptoms, and in 36 cases the lesions were ulcerated when first seen.

Frazell and Lucas,⁹⁶ in a review of 1,554 patients with this disease, present the following table showing the symptoms encountered in primary cases of lingual cancer (Table 26).

TABLE 26

PRESENTING SYMPTOMS IN PRIMARY CASES OF LINGUAL CANCER

Locat. Les.	No. Pt.	Vis./ Palp. Les	Loc. Pain	Dys- phagia	Lump in Neck
ANT. ² /3	902	696	266	32	58
POST. ¹ /3	303	46	138	83	94
TOTAL	1,205	742	404	115	152

Shafer, Hine and Levy³¹⁸ indicate that although pain is not a common complaint of initial cases of

cancer of the tongue, the majority of patients ultimately experience pain, particularly when the lesion is infected.

Of 330 patients with lingual cancer studied by Ariel,³ there was an average of 6.1 months from the time the patient first noted symptoms until the time he sought medical attention, and after the patient had consulted the physician, there was a further delay of 1.4 months until a diagnosis was established, giving an over-all delay of 7.5 months. Martin, Munster and Sugarbaker,²⁰¹ in a review of 556 patients with this disease, indicate that the average duration of symptoms before admission was about seven months. In the series of 54 hospital patients investigated by Sharp and Spickerman,³⁴⁶ the average delay before medical examination was 8.5 months, while in another separate series of 27 private patients, they report an average delay of 7.6 months.

Rahausen and Sayago,²⁸¹ in a study of 113 cases, observed that the average patient waited 6.3 months before consulting a physician, while Flamant et al.⁹⁵ record an average delay of 4.6 months in the 904 cases investigated by him.

CLINICAL APPEARANCE

According to Martin, Munster and Sugarbaker,²⁰¹ the manner of origin and subsequent development of lingual cancer vary, depending on its exact site of

origin. They indicate that lesions on the anterior two-thirds are initially small, indurated, painless, non-tender ulcers, and as they increase in size, the surfaces become raised and granular with accompanying severe ulceration and infiltration. Finally, the centres of these ulcers become excavated leading to deep erosion, fissuring, and infection with pain and tenderness, and the tongue become immobile. Repeated hæmorrhage, due to erosion of the lingual artery or its branches, and surface necrosis are apt to occur at this late stage of the disease.

Shafer, Hine and Levy,³¹⁸ and Ariel³ indicate that cancer of the tongue may begin as a superficially indurated lesion with slightly raised borders, and may develop into a bulky fungating exophytic mass, or as an infiltrative growth producing marked fixation and induration. Ariel³ adds that the lymphatics at the base of the tongue may occasionally be obstructed with cancer to produce a hideous macroglossia.

Baud³⁴ reports that lesions on the posterior third of the tongue begin as interstitial small growths with ulceration. These increase in size with accompanying deep infiltration and progressive invasion to involve the whole posterior third, with further extension forward to involve the anterior two-thirds of the tongue and posterior part of the floor of the mouth. Protrusion

of the tongue becomes more and more difficult as the disease advances.

Ariel³ indicates that cancer of the tip of the tongue or lateral margins has a tendency to remain localized until late stages of the disease when it invades adjacent portions of the oral cavity, including the mandible. Lesions on the dorsum of the tongue frequently infiltrate deep into the underlying musculature, while those on the central surface extend early to the floor of the mouth and mandible. On the other hand, cancer of the base of the tongue spreads early, rapidly, and extensively to neighbouring pharyngeal structures.

Reporting on the degree of local spread of lingual cancer, Flamant et al.,⁹⁵ in an analysis of 904 cases, indicate that 18 per cent. of the primary tumours were less than 2 cm. in diameter and localized, 33 per cent. were more than 2 cm. in diameter, but still localized, 39 per cent. were fixed, or limited the mobility of the tongue, or invaded one of the neighbouring organs, and 10 per cent. had progressed beyond the limits of the tongue and had invaded adjacent structures widely.

Cade and Lee⁶¹ report that of the 653 cases studied by them, only in half of this number was the primary lesion still confined to the tongue, and that

at least one-third of cases had spread to adjacent structures, usually the fauces or mouth floor.

HISTOPATHOLOGIC TYPES

Martin, Munster and Sugarbaker,²⁰¹ in a review of 556 cases of lingual cancer, report that differentiating keratinizing squamous cell carcinoma and relatively non-keratinizing mucous membrane types of epidermoid carcinoma comprise about 90 per cent. of malignant tumours of the anterior two-thirds of the tongue, while about 80 per cent. of carcinoma of the base of the tongue are of the non-keratinizing variety. They indicate that tumours of the posterior third of the tongue are generally more anaplastic, and transitional cell carcinoma and lymphoepithelioma comprise about 20 per cent. of tumours in this region of the tongue. They add that spindle cell carcinomas may occur in the tongue but they are rare, and certain forms of adenocarcinoma, adenoic cystic adenocarcinoma, and mucous gland adenocarcinoma may also be found, while sarcomas of the tongue are extremely rare, except for lymphosarcomas of the lingual tonsillar tissue.

The findings of Rahaussen and Sayago²⁸¹ in a review of 113 cases are as follows:

	<u>Cases</u>
EPIDERMOID CARCINOMA	
GRADE 1 and 2	85
GRADE 3 and 4	13
RECTICULUM SARCOMA	1
LYMPHOMA	1
NOT STATED	13
	113

As can be seen, most of the histopathologic types were differentiated squamous cell carcinoma of Broders' Grade 1 and 2.

Frazell and Lucas⁹⁶ state that, generally speaking, cancer of the tongue arises from the surface epithelium and, consequently, 97 per cent. of the tumours are of the squamous or epidermoid types of carcinoma. In their analysis of 1,554 cases they noted the following histologic types:

<u>Type of Tumour</u>	<u>No. Cases</u>	<u>%</u>
SQUAMOUS OR EPIDERMOID CARCINOMA	1,505	96.9
ADENOCARCINOMA	28	1.8
MISCELLANEOUS	21	1.3
LYMPHOMA	19	
LYMPHOANGIOSARCOMA	1	
RHABDOMYOSARCOMA	1	

They indicate that most of the tumours were in Grade II with occasional Grade I and Grade IV, and that

sarcomas of the tongue are rare.

In the series of 137 patients with carcinoma of the tongue investigated by Voutilainen and Tuovinen,³⁸¹ they report that 90 patients had squamous cell carcinoma, 14 had undifferentiated carcinoma, and there were 7 epidermoid carcinomas, 2 solenoid carcinomas, 2 basal cell carcinomas, and 2 reticular cell carcinomas.

METASTASES

Colby, Kerr and Robinson⁵⁰ and Shafer, Hine and Levy³¹⁸ state that metastases occur early and with great frequency in carcinoma of the tongue. Boyd²⁶ attributes the rapid spread to three factors:

1. The extremely rich lymphatic drainage of the tongue.
2. The constant muscular movements of the tongue.
3. The high grade of the tumour.

He adds that lymph spread takes place into the submental and submaxillary lymph nodes, the superior and inferior deep cervical nodes, and occasionally the supraclavicular nodes, and that in tumours of the posterior third of the tongue, the upper deep cervical group of nodes may be involved bilaterally.

Tiecke³⁶¹ claims that over half of the patients with cancer of the tongue have metastases to the cervical

lymph nodes at the time of treatment, and nearly a fourth have distant metastases during this time.

Ariel³ estimates that the incidence of metastases to regional lymph nodes in patients with cancer of the tongue is between 40 per cent. to 70 per cent. In an extensive review of the literature, he presents the following table summarising the reports of other authors regarding the incidence of such metastases (Table 27).

TABLE 27

INCIDENCE OF CERVICAL METASTASES ASSOCIATED WITH LINGUAL CANCER

Author	No. of Cases	% of Metastases on Admission	% of Metastases after Admission	% of metastases Total
BERVEN (1932)	104	-----	-----	42
BERVEN (1936)	82	-----	-----	65
MARTIN, MUNSTER and SUGARBAKER (1940)	556	35	25	60
CADE (1947)	220	-----	-----	59
HARNETT (1947)	287	-----	-----	56
WEYDE (1947)	145	38	19	56
JACOBSSON (1948)	277	48	12	60
GIBBEL, CROSS and ARIEL (1949)	208	68.8	-----	68.8

Source: ARIEL³

From the author's review of the literature, the following information concerning the incidence of metastases associated with cancer of the tongue are collected:

VOUTILAINEN and TUOVINEN³⁸¹ - Of 137 cases, 14 (10.2 per cent.) had metastases directly to the neck or chin, and 38 (27.7 per cent.) had distant metastases.

FRAZELL and LUCAS⁹⁶ - Of 1,554 cases, 40 per cent. had positive regional node metastases clinically, and of these, 20 per cent. were bilateral.

MARCIAL¹⁷⁹ - Of 439 patients, 206 (47.1 per cent.) had clinical metastases at the time of admission and, except for 11 patients (of the 206 cases) who had distant metastases, the rest were invariably limited to the cervical region.

PAYMASTER and SHROFF²⁴⁴ - Of 520 cases of cancer of the base of the tongue, 60 per cent. had palpable metastatic lymph nodes in the neck and, of these, 50 per cent. were bilateral.

RAHAUSEN and SAYAGO²⁸¹ - Of 113 patients, 67 (59.3 per cent.) had clinical metastases on admission, and an additional 18 (15.9 per cent.) developed regional lymph node metastases subsequently, giving a total of 75.2 per cent. who had metastases throughout some stage of the disease.

SHARP and SPICKERMAN³⁴⁶ - Of 81 cases, 44 (54.3 per cent.) had metastatic lymph nodes at the time of admission, and another 9 (11.1 per cent.) had metastases later on, giving a total of 65.4 per cent.

MARTIN, MUNSTER and SUGARBAKER²⁰¹ - Of 556 patients, 39 per cent. had metastases on admission, and an additional 24 per cent. subsequently had metastases. Bilateral metastases occurred in about 25 per cent. of all lesions which metastasized. In the autopsy records of 68 patients who died of the cancer, 12 (18 per cent.) had visceral metastases.

CADE and LEE⁶¹ - Of 518 cases, 298 (57.5 per cent.) developed metastatic node involvement when first seen, and an additional 97 (19 per cent.) developed metastases subsequently, giving a total of 76.5 per cent. who had metastases.

BERVEN³⁵ - of 136 treated patients with lingual cancer, 65 (47.8 per cent.) had clinical metastases, and in another separate series of 302 cases, 60 per cent. had metastases.

TREATMENT

Cancer of the tongue can be treated by either surgical or radiological methods. Shafer, Hine and Levy³¹⁸ state that the treatment of this disease presents a difficult problem and no specific conclusions can be drawn concerning the efficacy of surgery in comparison to radiotherapy. They feel that the judicious combination of the two methods will probably be of greatest benefit to the patient.