ORAL PRECANCEROUS LESIONS

Hetessy\textsuperscript{125} 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, Cahn\textsuperscript{47} 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,\textsuperscript{112} defines precancerses 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, Weisberger\textsuperscript{390} 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 Themann\textsuperscript{371} 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 Skolnik\textsuperscript{164}
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 Spickerman 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 Skolnik 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 Schwinne of Budapest in 1877.\textsuperscript{339, 369}

A review of the literature shows the confusion in the usage of this terminology. To some,\textsuperscript{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,\textsuperscript{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. Sprague 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. Shklar 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., Donaldson, and Smillie suggest that the use of the term leukoplakia should be discontinued altogether. As a substitute, Kollar and his colleagues 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. 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
Bernier\textsuperscript{16} 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 Tiecke\textsuperscript{360} differentiate this from the innocuous lesion without the characteristic of dyskeratosis, which they termed pachyderma oris.

Smillie\textsuperscript{314} 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,\textsuperscript{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:

\textbf{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.

Shklar\textsuperscript{303} 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

\textbf{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,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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, Paymaster\textsuperscript{242} reports that 30 per cent. had leukoplakia, and this corresponds to the findings of McGrath and Schimdt\textsuperscript{182} in their series of 117 patients.

Sharp and Hazlet,\textsuperscript{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 Weisberger\textsuperscript{390} reports a 60 per cent. coexistence of leukoplakia and oral cancer in 275 patients.

The findings of Archer and Morris\textsuperscript{9} was that 15.8 per cent. of 203 patients with oral malignancy had leukoplakia, while Meyer and Shklar\textsuperscript{185} 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 Waldron indicate that in the older literature this was estimated to be about 30 per cent., but in their series, and that of Cooke and Renstrup, the incidence of such malignant transformation in leukoplakia was much lower.

Hahn, Morgenroth and Themann 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 Skolnik 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, Hobaek reports that in 16 per cent. of cases the carcinomatous lesions developed from pre-existing leukoplakia. This
<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>Author</th>
<th>No. of Patients with the cancer</th>
<th>Percentage of Leuko-plakia</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIP</td>
<td>WARD and HENDRICK(^401)</td>
<td>259</td>
<td>17</td>
</tr>
<tr>
<td>LIP</td>
<td>CROSS, GURALNICK and DALAND(^65)</td>
<td>563</td>
<td>14.5</td>
</tr>
<tr>
<td>LIP</td>
<td>SMITH(^331)</td>
<td>129</td>
<td>11</td>
</tr>
<tr>
<td>LIP</td>
<td>SCHREINER and CHRISTY(^302)</td>
<td>636</td>
<td>2.4</td>
</tr>
<tr>
<td>TONGUE</td>
<td>ARIEL(^3)</td>
<td>---</td>
<td>10 to 40</td>
</tr>
<tr>
<td>TONGUE</td>
<td>RAHAUSEN and SAYAGO(^281)</td>
<td>113</td>
<td>11</td>
</tr>
<tr>
<td>TONGUE</td>
<td>TRIEGER et al.(^365)</td>
<td>108</td>
<td>14.8</td>
</tr>
<tr>
<td>TONGUE</td>
<td>PAYMASTER and SHROFF(^244)</td>
<td>700</td>
<td>32</td>
</tr>
<tr>
<td>FLOOR OF THE MOUTH</td>
<td>MARTIN and SUGARBAKER(^197)</td>
<td>103</td>
<td>25</td>
</tr>
<tr>
<td>FLOOR OF THE MOUTH</td>
<td>GARDNER, BOWEN and BROWN(^106)</td>
<td>28</td>
<td>3.5</td>
</tr>
<tr>
<td>BUCCAL MUCOSA (CHEEK)</td>
<td>MARTIN and PFLUEGER(^200)</td>
<td>99</td>
<td>22</td>
</tr>
<tr>
<td>BUCCAL MUCOSA (CHEEK)</td>
<td>PAYMASTER(^21)</td>
<td>650</td>
<td>20</td>
</tr>
<tr>
<td>BUCCAL MUCOSA (CHEEK)</td>
<td>JACKSON and NEW(^142)</td>
<td>107</td>
<td>15</td>
</tr>
<tr>
<td>BUCCAL MUCOSA (CHEEK)</td>
<td>O'BRIEN and CATLIN(^238)</td>
<td>248</td>
<td>18</td>
</tr>
<tr>
<td>BUCCAL MUCOSA (CHEEK)</td>
<td>JORSTAD(^144)</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>PALATE</td>
<td>MARTIN(^199)</td>
<td>74</td>
<td>27</td>
</tr>
<tr>
<td>GINGIVA</td>
<td>WILKINS and VOGLER(^406)</td>
<td>81</td>
<td>40</td>
</tr>
</tbody>
</table>
corresponds closely to the findings of Pindborg, 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, he 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 Schour 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 Strickland 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 Hazlet indicate that taking a time factor as a guide to assess the potentiality of malignant degeneration is not reliable,
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>No. of Patients Observed</th>
<th>Rate of Malignant Transformation %</th>
<th>Observation Period years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKACH, SVOBODA and KUBAT</td>
<td>Poland</td>
<td>1960</td>
<td>71</td>
<td>1.4</td>
<td>3-6</td>
</tr>
<tr>
<td>SUGAR and BANOCZY</td>
<td>Hungary</td>
<td>1959</td>
<td>86</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>STURGIS and LUND</td>
<td>United States</td>
<td>1934</td>
<td>298</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>LEONARDELLI and TALAMAZZI</td>
<td>Italy</td>
<td>1950</td>
<td>268</td>
<td>20</td>
<td>1 month - 15 years</td>
</tr>
<tr>
<td>WEISBERGER</td>
<td>United States</td>
<td>1957</td>
<td>22</td>
<td>36</td>
<td>4</td>
</tr>
</tbody>
</table>

Source: PINDBORG\textsuperscript{251}
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.

Weisberger\textsuperscript{390} 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.

Bhaskar\textsuperscript{28} estimates that 25 per cent. of patients with leukoplakia will develop a malignancy at the sites where the leukoplakic lesions are present. Pindborg\textsuperscript{250} 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.

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

Bruszt (quoted by Pindborg) 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, 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.

Pindborg 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.
TABLE 12

FREQUENCY OF ORAL LEUKOPLAKIA IN DIFFERENT LOCALITIES, INDIA

<table>
<thead>
<tr>
<th>Locality</th>
<th>No of patients examined</th>
<th>Percentage with leukoplakia</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUCKNOW (Uttar Pradesh)</td>
<td>10,000</td>
<td>3.3</td>
</tr>
<tr>
<td>BOMBAY (Maharashtra)</td>
<td>10,000</td>
<td>2.8</td>
</tr>
<tr>
<td>BANGALORE (Mysore)</td>
<td>5,612</td>
<td>1.6</td>
</tr>
<tr>
<td>TRIVANDRUM (Kerala)</td>
<td>2,000</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Source: PINDBORG\textsuperscript{251}

SEX INCIDENCE

The consensus of opinion is that leukoplakia of the oral cavity is more prevalent among men than in women\textsuperscript{106, 170, 390, 395, 398} Bernier\textsuperscript{16} and Knutson\textsuperscript{150} 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).

Castigliano\textsuperscript{51} 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\textsuperscript{150, 164, 395, 398} indicate that oral leukoplakia is seen more commonly in persons of older age group. Castigliano,\textsuperscript{51} Lucas,\textsuperscript{170}
TABLE 13
SEX DISTRIBUTION OF ORAL LEUKOPLAKIA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Report</th>
<th>Percentage Men</th>
<th>Percentage Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOBÆK</td>
<td>1946</td>
<td>73.6</td>
<td>26.4</td>
</tr>
<tr>
<td>RENSTRUP</td>
<td>1958</td>
<td>66.0</td>
<td>34.0</td>
</tr>
<tr>
<td>LEDERER and SKOLNIK</td>
<td>1959</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>SHAFER and WALDRON</td>
<td>1961</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>PINDborg</td>
<td>1963</td>
<td>59</td>
<td>41</td>
</tr>
</tbody>
</table>

Bernier,\textsuperscript{16} and Weisberger\textsuperscript{390} share the opinion that this condition is seen predominantly in the fourth and fifth decades of life.

Waldron and Shafer,\textsuperscript{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,\textsuperscript{280} who, in a smaller review of 90 cases, reports that 90 per cent. of the patients were over 40 years old.

Hobaek,\textsuperscript{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 Levy\textsuperscript{318} 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:

RENSTRUP\textsuperscript{280} - buccal mucosa and commissures, alveolar mucosa, tongue, lip, hard and soft palate, floor of the mouth, and gingivae.

SHARP, BULLOCK and HAZLET\textsuperscript{323} - tongue, buccal mucosa, gingivae, hard palate, and lips.

HOBAEK\textsuperscript{127} - tongue and floor of the mouth, lower lip, buccal mucosa, palate and gingivae.

SHAFER and WALDRON\textsuperscript{319} - 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.

CASTIGLIANO\textsuperscript{51} - 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 LEVY^318
Pindborg,\textsuperscript{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**

<table>
<thead>
<tr>
<th>Localization</th>
<th>LUCKNOW 328 patients with 510 leukoplakias</th>
<th>COPENHAGEN 211 patients with 373 leukoplakias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labial commissure</td>
<td>48.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Buccal Mucosa</td>
<td>40.1</td>
<td>42.9</td>
</tr>
<tr>
<td>Lips</td>
<td>4.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Alveolar Ridge</td>
<td>3.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Tongue</td>
<td>2.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Gingiva</td>
<td>0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Palate</td>
<td>0.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Floor of Mouth</td>
<td>-</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: PINDBORG\textsuperscript{260}

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. Pindborg\textsuperscript{260} 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. Weisberger 390 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 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. On the other hand, Shafer, Hine and Levy 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, Cooke, and Renstrup 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. This is based mainly on the findings that vitamin A deficiency will induce metaplasia and keratinization of certain epithelial surfaces. Shafer, Hine and
Levy 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. MacComb 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, in treating 65 women patients who had leukoplakia with estrogenic hormones, reports that the results obtained were encouraging. Shafer, Hine and Levy draw attention to the lack of investigation in this field, which makes it difficult to evaluate its etiologic significance.

Hertz regards galvanism as of importance in the etiology of leukoplakia. However, in recent years, there is a tendency to discount such a relationship.

Most of the factors enumerated so far seem to be capable of promoting oral leukoplakia, mainly through chronic irritation to the mucosal surface. However, Cooke points out that leukoplakia is also seen in the mouths of non-juvenile 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,\textsuperscript{390} and Sharp, Bullock and Hazlet.\textsuperscript{323}

Swan,\textsuperscript{343} in an extensive review of the literature, summarizes 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.

Hobaek\(^{127}\) 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 Levy\(^{318}\) 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.

Bernier\(^{16}\) 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 Bhaskar\(^{28}\) describes the lesions clinically as a white, flat or raised, rough or smooth patches of varying sizes, which sometimes present ulceration.
Chromet, Niebel and Valaitis 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 Skolnik broadly divide leukoplakia into three forms, namely, the smooth variety, the raised (plaque) type, and the verrucous or papillomatous form, while Pindborg 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, leukoplakic lesions may be opaque, thick or thin, white, hornified, leathery plaques, exhibiting various degree of irregularity and roughness of the surface.

Renstrup 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 Levy 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 keratoses, leukokeratosis, hyperkeratosis, hyperkeratosis complex, hyperkeratosis simplex, non-specific keratoses, 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 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, phemphigus, erythema multiforme, herpes simplex, and early epidermoid carcinoma.

Although a differential diagnosis from such an exhaustive list is not easy, a carefully and systematic approach is important, utilising 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. Castiglione 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.

Hobaek\textsuperscript{127} 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.

Shira\textsuperscript{357} 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.

MacComb\textsuperscript{178} 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 Skolnik also advocate conservative treatment as the first approach before any radial 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.

Bernier and Bhaskar 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.

Waldron indicates that in lesions which exhibit significant cellular atypia, excision, stripping or fulguration 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 Levy\textsuperscript{318} 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.

Sharp\textsuperscript{321} 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 desiccated liver, vitamin B\textsubscript{12}, 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.\textsuperscript{51, 321, 390} It is also sometimes
termed Kelly-Patterson syndrome because of studies made by them in 1919. There is unanimous agreement by several investigators that this syndrome is a precancerosis. Ahlbom 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.

Weisberger 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. Wynder et al. 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 Levy indicate that women suffering from this syndrome are usually in their fourth and fifth decades of life, while Ahlbom gives a wider age range of from 15 to 50 years.

Patients suffering from Plummer Vinson syndrome present various clinical signs and symptoms. These include dysphagia, long-standing hypochromic mycrocytic 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, alchorrhedria, 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 dypsnea, excessive menstrual bleeding, and
occasional kraurosis.

Ahlbom, Uthman, and Shafer, Hine, and Levy, 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 achlorhydria 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 Levy 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. indicates that the dysphagia itself, if not due to web formation, may frequently be due to the atrophic changes of the musculature of the oesophagus 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. Weisberger\textsuperscript{390} 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\textsuperscript{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. Ahlbom\textsuperscript{8} 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.\textsuperscript{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, the diagnosis of Plummer Vinson Syndrome is based on the patient's history and haematologic findings. Uthman 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

- Dysphagia
  - Predisposition to carcinoma of upper alimentary tract
  - Atrophic changes in oral mucosa and esophagus
    - Anemia
    - Low serum iron
    - Koilonychia
    - Glossitis
    - Edentia
    - Oral fissure

- Iron deficiency state
  - Loss of iron in pregnancy, menstruation, etc.
  - Achlorhydria
  - Atrophic changes in gastric mucosa

- Marginal intake of iron
  - And/or
  - Defective absorption of iron

- Marginal intake of other nutrients or presence of a toxic dietary factor
  - Deficiency of unknown nutrients

Closed boxes indicate factors known to coexist in Plummer-Vinson syndrome. Solid lines indicate relationships held to be reasonably certain. Broken lines indicate relationships 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 Skolnik\textsuperscript{164} 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 Levy\textsuperscript{318} report that the anaemia usually responds satisfactorily to iron therapy and a high protein diet, while Weisberger\textsuperscript{390} 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 Levy\textsuperscript{318} 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 Hazlet 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, 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 Levy state that the etiology of leukoedema is unknown. The study of Sandstead and Lowe 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, 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 Skolnik 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, Rose, Castigliano,
Hetessy and Thoma who indicate that malignant degeneration of papillomas is feasible, and they
should be regarded as precancerous.
On the other hand, Gorlin 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 carcinoma. Toto indicates that papillomas are generally benign, but they may exhibit acanthosis and, very rarely, dyskeratosis with malignant degeneration, while Shafer, Hine and Levy express that such a possibility is fairly remote.

Shklar 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, clinically, papillomas are exophytic growths with a firm, stalk-like base. However, Lederer and Skolnik 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 Levy 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.\textsuperscript{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.\textsuperscript{129, 318} Thoma\textsuperscript{368} 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.\textsuperscript{150} This view is shared by Lederer and Skolnik,\textsuperscript{164} Hertz,\textsuperscript{112} Castigliano,\textsuperscript{51} and Thoma.\textsuperscript{368}

Hetessy,\textsuperscript{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 Levy 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)**

Hertz and Robinson are of the opinion that papillary hyperplasia should be regarded as precancerous, while Lambsen and Shafer, Hine and Levy indicate that because of its malignant potential, this condition should not be considered as entirely harmless. Thoma 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. Lambsen surveyed 226 denture wearing patients and reports that the prevalence of this condition was 11 per cent. He
indicates that relief areas in dentures 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 Levy\textsuperscript{318} 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.\textsuperscript{177, 318} The surface morphology of another type of papillary hyperplasia is mossy or velvet-like.\textsuperscript{177}

According to Shafer, Hine and Levy,\textsuperscript{318} histologically, the numerous projections each has a stratified squamous epithelial covering and a central core of connective tissue. They share with Robinson 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, Thoma\textsuperscript{368} 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.

Robinson and Shafer, Hine and Levy 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. 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.

Pindborg 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, 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.\textsuperscript{106, 318}

Shafer, Hine and Levy\textsuperscript{318} indicate that essentially this is an intraepithelial carcinoma, except that invasion of the underlying tissues occur earlier. On the other hand, Hertz\textsuperscript{112} regards this condition as a precursor of leukoplakia and indicates that it is frequently mistaken as such.

Sprague\textsuperscript{306} 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,\textsuperscript{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, 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 Levy point out that the "junctional activity" displayed by junctional nevi has serious implications, since this form of nevi frequently undergo malignant transformation into melanomas.

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

Pindborg\textsuperscript{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,\textsuperscript{251, 260, 262} Pindborg and Zachariah,\textsuperscript{261} Pindborg et al.,\textsuperscript{263, 264} Paymaster,\textsuperscript{241} Paymaster and Gangadharam,\textsuperscript{242, 253} and Rao.\textsuperscript{284}

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

In another investigation of this condition in South India, Pindborg and Zachariah\textsuperscript{261} 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,\textsuperscript{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

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

Source: PINDBORG²⁶⁰, 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 Pindborg²⁶⁰, 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,\textsuperscript{284} submucous fibrosis may be a manifestation of disordered growth of collagen. Pindborg\textsuperscript{260,262} indicates that the basic change in this condition is a fibro-elastic transformation of the lamina propria connective tissue with epithelial atrophy, and is occasionally preceded by visicle formation. As the fibrosis progresses, the oral mucous membrane exhibits stiffness, and trismus eventually occurs which may cause difficulties in chewing, swallowing and speaking.

Rao\textsuperscript{284} 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\textsuperscript{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., 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, but in contrast, a peripheral eosinophilia was not significant in Pindborg's findings.

With regard to treatment of this condition, Pindborg et al. indicate that several methods of therapy have been tried which include surgical cutting of the fibrotic bands, and/or injection of fibrolysis, gold, or vitamins A and E. Rao 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 CANCER

HISTOPATHOLOGY

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. Castiglione, 51 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 degrees 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 varia-
rious, actively invading the adjacent connective tissue.

**GRADING**

The varying degrees of differentiation, as
seen in epidermoid carcinoma, is utilised by Broders 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.

Broders 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 Levy 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.

Ueno 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,\textsuperscript{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,\textsuperscript{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 without 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,\textsuperscript{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 inoculation

Lee McGregor\textsuperscript{225} 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

Copeland\textsuperscript{71} 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., 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 Levy 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.

Castigliano 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 Martin 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.

Paymaster\textsuperscript{241} 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Total Number of Patients</th>
<th>Cervical Metastasis No.</th>
<th>%</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GARDNER, LOVE and HAMBERGER105</td>
<td>189</td>
<td>-</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td>GARDNER117</td>
<td>167</td>
<td>-</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>SIMONS, MASSON and BEAHRS352</td>
<td>150</td>
<td>79</td>
<td>53</td>
<td>histologically proved</td>
</tr>
<tr>
<td>MUSTARD and IRVING218</td>
<td>1,177</td>
<td>630</td>
<td>53.6</td>
<td>either clinical or pathologic evidence</td>
</tr>
<tr>
<td>LEFFALL and WHITE165</td>
<td>107</td>
<td>68</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>WOOKEY et al.411</td>
<td>1,963</td>
<td>572</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>COGBILL73</td>
<td>82</td>
<td>50</td>
<td></td>
<td>microscopic evidence</td>
</tr>
</tbody>
</table>

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. Others138, 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.

Lucas,\textsuperscript{170} and Gowen and de Suto-Nagy\textsuperscript{120} 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 Topazian\textsuperscript{363} 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, Castigliano\textsuperscript{51} 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.

Martin\textsuperscript{180} states that in uncontrolled cancer of the mouth, metastasis invariably occurs to some viscus below the clavicles such as the lungs, liver, or bones. Hoye\textsuperscript{138} 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

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

Source: HOYE 138
From his own autopsy study of 42 patients who died of epidermoid carcinoma of the head and neck, Hoye reports that 23 (55 per cent.) were found to have distant metastases. This parallels the findings of Gowen and de Suto-Nagy, 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) - 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) - 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) - 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)\textsuperscript{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)\textsuperscript{105} - Of 189 cases of oral malignancy, 14.8 per cent exhibited distant metastases.

COLEMAN (1965)\textsuperscript{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)\textsuperscript{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,\textsuperscript{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 underestimate 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 Rominger 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-Nagy 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.

Topazian 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. Boyd 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, 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 Holder 278 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-Nagy 120 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, Topazian 363 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. Hoye\textsuperscript{138} is of the opinion that the grade of the primary tumour has some correlation with the subsequent development of distant metastases.

Topazian\textsuperscript{363} states that in general, the metastases tend to reproduce the histologic structure of the primary tumour, while Gower and de Szüto-Nagy\textsuperscript{120} 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. Thoma measures feels that a close co-operation of the surgeon, the radiotherapist, and the pathologist is essential in the treatment of this disease.

James 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.

Murray et al. 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. Boyd 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. Murray et al. 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 are of the opinion that in many instances fairly radical surgery is essential to effect a cure. They and Behrns and Barber 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 Chambers 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 the surgical mortality ranges from 1.5 per cent. to 11 per cent.

Simon, Masson and Beahrs 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 Chambers 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. Des Prez et al. 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, 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 James 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. McLaren 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. 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.

James 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 situations.

According to James, 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 gold$^{198}$ are frequently used to supplement external high voltage therapy. Delclos 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. Pointon indicates that this type of treatment is very suitable for anterior lesions arising in the floor of the mouth with minimal tongue involvement.

Declos 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. Pointon\textsuperscript{267} 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.

Thoma\textsuperscript{368} 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 supervoltage therapy. Easson\textsuperscript{87} 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 Theratron\textsuperscript{60} Co. unit, as listed by various authors,\textsuperscript{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.\textsuperscript{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.\textsuperscript{286}

According to Boyd,\textsuperscript{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.

Boyd 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. Novack 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. 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 Drone\(^{287}\) 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 McLaren\(^{220}\) 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.

Thoma\(^{368}\) 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 others\(^{287}\) advocate the extraction of all teeth in the affected segment, or a complete extraction in neglected mouths prior to irradiation. Rahn and Drone\(^{287}\) 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. Thoma\(^{368}\) 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 Drone 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 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, Strickland claims that the flow of saliva nearly always returns to a sufficient amount within six months of irradiation.

Frank, Herdley, and Philippe 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. Delclos 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,\textsuperscript{103} and James\textsuperscript{141} 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. Thoma\textsuperscript{368} indicates that these shields are essentially prosthetic appliances into which is incorporated a lead sheet (1/8th of an inch thick) cut and shaped to fit over the irradiated area.

**ELECTROCOAGULATION**

Meyer\textsuperscript{221} states that electrosurgery has a definite place in the management of premalignant and malignant lesions of the oral cavity. This opinion is shared by Thoma\textsuperscript{318} 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.

Meyer\textsuperscript{221} 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. \textsuperscript{221, 368}

\textbf{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. Karnofsky\textsuperscript{158} 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 Tucker\textsuperscript{133} 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.

Larionov\textsuperscript{173} 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 deoxyri- bonucleic 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, and Gaisford 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 Tucker 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 ethoglucidc and cyclophosphamide are superior in the treatment of head and neck malignancy. In their series of 80 cases of advanced head and neck cancer threatened with ethoglucidc 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 studies, 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 testerone, or in those cases treated previously by radiation therapy. In the hands of Harrison and
Tucker, the use of methotrexate in the treatment of advanced head and neck cancer was reported to be disappointing, while Karnofsky 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.

Others 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, 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. Farber 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. 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 bloodstream. They report that definite gross and microscopic destruction of advanced neoplasms was achieved using such a technique. Nitrogen mustard was used by Golomb and Wright in the combination, while Harrison and Tucker employed cyclophosphamide and ethoglucide in this regard.

Larionov 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.

Feind\textsuperscript{98} 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.,\textsuperscript{202} and Martin,\textsuperscript{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 sternamastoid 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 authorities71, 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 difference 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 considerably 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 Behr's and Barber 41 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 Frazell 223 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, 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 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, Martin and his associates, Copeland, and McLaren who feel that an operation of such magnitude should only be undertaken if there is a definite indication for it. Martin et al., 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 Copeland 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. Lovely 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.

Meyer 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. 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.

Moore 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 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 Daland \(^{65}\) 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 Nelson \(^{233}\) 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 Hazlett \(^{323}\), the lips are the most frequent site of intraoral carcinomas. Castigliano \(^{51}\) indicates that carcinoma of the lip consists of 31 per cent. of all oral carcinomas. While Ariel \(^{2}\) 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, Gardner \(^{117}\) 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, who report a 98 per cent. male incidence in a study of 563 patients with this disease. Similar findings are reported by Welch and Nathanson 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, and Nelson.

According to Bernier and Bourgoyne (quoted by Gardner et al.), 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>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total No. of Cases</th>
<th>Number of Male</th>
<th>Number of Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCHREINER and CHRISTY</td>
<td>1942</td>
<td>636</td>
<td>619</td>
<td>17</td>
</tr>
<tr>
<td>WIDMAN</td>
<td>1950</td>
<td>363</td>
<td>359</td>
<td>4</td>
</tr>
<tr>
<td>WARD and HENDRICK</td>
<td>1950</td>
<td>259</td>
<td>251</td>
<td>8</td>
</tr>
<tr>
<td>NELSON</td>
<td>1955</td>
<td>742</td>
<td>699</td>
<td>43</td>
</tr>
<tr>
<td>SMITH</td>
<td>1960</td>
<td>129</td>
<td>117</td>
<td>12</td>
</tr>
</tbody>
</table>

Ariel 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 Ariel\(^2\) 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\textsuperscript{26, 50, 51, 233, 318, 368} are that the lower lip is more frequently involved in cancer than the upper lip. Bhaskar\textsuperscript{28} and Bernier\textsuperscript{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,\textsuperscript{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).

Bhaskar\textsuperscript{28} and Castiglione\textsuperscript{51} 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,\textsuperscript{15, 16} Ariel,\textsuperscript{2} and Colby, Kerr and Robinson\textsuperscript{50}, report that the vermilion border is the site of most frequent occurrence. On this issue,
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total No. of Cases</th>
<th>No. on Upper Lip</th>
<th>No. on Lower Lip</th>
</tr>
</thead>
<tbody>
<tr>
<td>WELCH and NATHANSON\textsuperscript{403}</td>
<td>1937</td>
<td>990</td>
<td>41</td>
<td>949</td>
</tr>
<tr>
<td>SCHREINER and CHRISTY\textsuperscript{302}</td>
<td>1942</td>
<td>636</td>
<td>22</td>
<td>614</td>
</tr>
<tr>
<td>WARD and HENDRICK\textsuperscript{401}</td>
<td>1950</td>
<td>259</td>
<td>20</td>
<td>239</td>
</tr>
<tr>
<td>NELSON\textsuperscript{233}</td>
<td>1955</td>
<td>742</td>
<td>50</td>
<td>692</td>
</tr>
<tr>
<td>SMITH\textsuperscript{331}</td>
<td>1960</td>
<td>129</td>
<td>5</td>
<td>124</td>
</tr>
</tbody>
</table>

Atkinson et al.,\textsuperscript{7} in their investigation of oral cancer in Papua and New Guinea, indicate that the majority of lip cancers in New Guineans are commissural 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. Boyd\textsuperscript{26} and Bernier\textsuperscript{16} 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 Widman reports that 40 per cent. of a group of 363 patients with this disease reviewed by them were pipe smokers. On the other hand, Ariel 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, and Castiglione are of the opinion that syphilis is of etiologic significance in lip cancer, the findings of Cross, Guralnick and Daland (7.2 per cent. of 563 patients had a positive Wasserman reaction), Widmann (8 per cent. of 363 cases had syphilis), and Schreiner and Christy (3.6 per cent. of 636 cases had syphilis) are suggestive of the minor role played by syphilis in cancer of the lip. Ariel 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 Daland are of the opinion that trauma superimposed on a background of poor oral hygiene may be of importance as an etiologic 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, 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 Christy 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. Boyd\textsuperscript{26} 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 Ariel\textsuperscript{2}) 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,\textsuperscript{16} Ward and Hendrick,\textsuperscript{401} and is substantiated by the findings of Schreiner and Christy\textsuperscript{302} 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 Hazlet\textsuperscript{323} 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, Wynder, Feldman and Bross,\textsuperscript{394, 395} Cahn,\textsuperscript{47} Bhaskar,\textsuperscript{28} and Shafer, Hine and Levy.\textsuperscript{318}

Ariel\textsuperscript{3} indicates that in cancer of the lip, leukoplakia, keratoses, cheilitis, and fissuring are commonly noted. Ward and Hendrick,\textsuperscript{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 Daland\textsuperscript{65} who indicate that 14.5 per cent. of 563 patients with lip cancer had leukoplakia and keratosis, while Smith,\textsuperscript{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 Christy\textsuperscript{302} 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,\textsuperscript{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 Schuchardt\textsuperscript{55} 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,\textsuperscript{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.

Smith\textsuperscript{331} 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 Hendrick\textsuperscript{401} 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,\textsuperscript{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**

Smith\(^{331}\) 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.

Ariel\(^{2}\) 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, in an analysis of the histopathology of 259 cases, presents the following distribution of graded lesions:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>119</td>
<td>46%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>51</td>
<td>20%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>25</td>
<td>10%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>Not graded</td>
<td>61</td>
<td>23%</td>
</tr>
</tbody>
</table>

Gardner, Schwartz and Pallen indicate that carcinoma of the upper lip grows more rapidly than carcinoma of the lower lip. This opinion is shared by Ariel 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, Ariel, Boyd, and Colby, Kerr and Robinson state that carcinoma of the lip is generally slow to metastasize, while Thoma claims that the development of metastases occur early in the course of the disease.

In a review of 563 cases, Cross, Guralnick and Daland observed that 113 patients had metastatic regional lymph nodes involvement, while Ward and Hendrick, in an analysis of 259 cases, report that 119 patients had palpable nodes. Ariel 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 Modlin\textsuperscript{213} is as follows (Table 20).

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metastases on admission</td>
<td>158</td>
<td>88.8</td>
</tr>
<tr>
<td>Metastases on admission</td>
<td>21</td>
<td>11.7</td>
</tr>
<tr>
<td>Metastases during follow-up</td>
<td>15</td>
<td>9.6</td>
</tr>
<tr>
<td>Total Metastases (5 year follow up)</td>
<td>36</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>179</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: MODLIN\textsuperscript{213}

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.\textsuperscript{2, 15, 50, 318} Thoma\textsuperscript{368} 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 Levy\textsuperscript{318} 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. Ariel\textsuperscript{2} indicates that there is a rather high incidence of crossed metastasis, because of the abundance of cross anatomoses in the lymphatic drainage in the mid-line of the lip.

According to Boyd\textsuperscript{26} and Bernier,\textsuperscript{15} metastasis occurs mainly via the lymphatics and seldom by the bloodstream. Widman\textsuperscript{400} claims that lesions involving the buccal commissures and buccal mucosa metastasize earlier and more frequently, while Ariel\textsuperscript{2} indicates that upper lip cancers show a greater tendency to metastasize to regional lymph nodes.

Ariel\textsuperscript{2} 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,\textsuperscript{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, \textsuperscript{318} Boyd, \textsuperscript{26} and Ariel\textsuperscript{2} are of the opinion that in skilled hands, surgery and X-ray irradiation give comparable results. This view is shared by Schreiner and Christy, \textsuperscript{302} but they indicate that the cosmetic results following irradiation are superior to those with surgery.

Bernier\textsuperscript{15} 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, \textsuperscript{401} Thoma, \textsuperscript{368} and Cross, Guralnick and Daland.\textsuperscript{65}

Thoma\textsuperscript{368} 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 Hendrick\textsuperscript{401} 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 Daland 65 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 Hendrick 401 indicate that electro-surgery may be used in cancers involving the entire lower lip to the mandible.

On the other extreme, Widman 400 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.
Ariel\(^2\) 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, Ariel\(^2\) 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 Broders' 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, Ariel\(^2\) 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.
Ariel \(^2\) 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>
<thead>
<tr>
<th></th>
<th>Three Year Cures (per cent.)</th>
<th>Five Year Cures (per cent.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY GROUP</td>
<td>180</td>
<td>76</td>
</tr>
<tr>
<td>SURGERY</td>
<td>72</td>
<td>93</td>
</tr>
<tr>
<td>IRRADIATION</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>COMBINED</td>
<td>39</td>
<td>58</td>
</tr>
<tr>
<td>SECONDARY GROUP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL METHODS</td>
<td>.79</td>
<td>66</td>
</tr>
<tr>
<td>TOTAL NUMBER</td>
<td>259</td>
<td>74.9</td>
</tr>
</tbody>
</table>

SOURCE: WARD & HENDRICK

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

Widman, 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 Christy who treated 636 cases mainly by X-rays and radium.

Cross, Guralnick and Daland report that the total cure rate for 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 Nathanson 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, Boyd, and Colby, Kerr and Robinson, the general prognosis of patients with lip cancer is regarded as good. This opinion is shared by Kremen and Arhelger 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,3 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:

Ariel 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 Daland 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 Levy and Ariel, the presence of metastases to the lymph nodes markedly influences the prognosis. Cross, Guralnick and Daland 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, Widman 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, 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, Ariel\textsuperscript{2} 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 Daland\textsuperscript{65} 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\textsuperscript{318} and Cross, Guralnick and Daland\textsuperscript{65} 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 Sugarbaker\textsuperscript{201} 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 Shroff\textsuperscript{244} 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.

Marcial\textsuperscript{179} 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 Sayago\textsuperscript{281} 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,\textsuperscript{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, 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, 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.

Ariel 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>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYSTROM</td>
<td>1922</td>
<td>Sweden</td>
<td>1 per 100,000</td>
</tr>
<tr>
<td>LEVIN</td>
<td>1944</td>
<td>New York State</td>
<td>3 per 100,000</td>
</tr>
<tr>
<td>TOD</td>
<td>1948</td>
<td>England</td>
<td>3 per 100,000</td>
</tr>
<tr>
<td>JACOBSSON</td>
<td>1948</td>
<td>Sweden (Radium-hemmet)</td>
<td>1/2 per 100,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Per. cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYSTROM</td>
<td>1911-12</td>
<td>Sweden</td>
<td>0.9 of 6,517cancers</td>
</tr>
<tr>
<td>PACK and</td>
<td>1917-29</td>
<td>New York City (Memorial Hosp.)</td>
<td>4.8 of 16,565</td>
</tr>
<tr>
<td>LEFEVRE</td>
<td></td>
<td></td>
<td>&quot;</td>
</tr>
<tr>
<td>HARNETT</td>
<td>1938-39</td>
<td>England</td>
<td>1.9 cancers</td>
</tr>
<tr>
<td>KHANOLKAR</td>
<td>1941-43</td>
<td>India</td>
<td>1.8 of 2,880cancers</td>
</tr>
<tr>
<td>JACOBSSON</td>
<td>1931-42</td>
<td>Sweden (Radium-hemmet)</td>
<td>1.8 of 15,388</td>
</tr>
<tr>
<td>GIBBEL, CROSS</td>
<td>1936-46</td>
<td>Hines, Illinois</td>
<td>1.8 of 17,327</td>
</tr>
<tr>
<td>ARIEL</td>
<td></td>
<td></td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Source: ARIEL 3

According to Bernier 16 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
Pallen\textsuperscript{119} indicate that in their studies the tongue was the most common location of oral carcinoma, only 27.5\textper 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,\textsuperscript{117} he observed that 28 per cent. were located on the tongue. On the other hand, Ueno et al.,\textsuperscript{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 Robinson\textsuperscript{50} claim that carcinoma of the tongue is the second most frequent form of oral cancer. This view is shared by Castigliano\textsuperscript{51} who states that cancer of the tongue accounts for 24.5 per cent. of all oral cancer. On the other hand, Shafer, Hine and Levy\textsuperscript{318} 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 Levy\textsuperscript{318} 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,\textsuperscript{3} in an extensive review of the literature, presents the following
table showing the sex incidence of this disease (Table 23).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Report</th>
<th>No. of Cases</th>
<th>% of Women</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHRLICH</td>
<td>1909</td>
<td>64</td>
<td>2</td>
<td>Austria</td>
</tr>
<tr>
<td>RICHARDS</td>
<td>1942</td>
<td>167</td>
<td>20</td>
<td>Canada</td>
</tr>
<tr>
<td>VIDEBACK</td>
<td>1945</td>
<td>---</td>
<td>37</td>
<td>Denmark</td>
</tr>
<tr>
<td>HARNETT</td>
<td>1947</td>
<td>287</td>
<td>14</td>
<td>England</td>
</tr>
<tr>
<td>MUSTAKALLIO</td>
<td>1948</td>
<td>202</td>
<td>49</td>
<td>Finland</td>
</tr>
<tr>
<td>SEBILEAU</td>
<td>1930</td>
<td>---</td>
<td>5</td>
<td>France</td>
</tr>
<tr>
<td>PETERS</td>
<td>1920</td>
<td>48</td>
<td>17</td>
<td>Germany</td>
</tr>
<tr>
<td>KHANOLKAR</td>
<td>1944</td>
<td>522</td>
<td>8</td>
<td>India</td>
</tr>
<tr>
<td>SIMEONI</td>
<td>1934</td>
<td>---</td>
<td>10</td>
<td>Italy</td>
</tr>
<tr>
<td>WASSINK</td>
<td>1935</td>
<td>---</td>
<td>15</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>WEYDE</td>
<td>1947</td>
<td>---</td>
<td>36</td>
<td>Norway</td>
</tr>
<tr>
<td>PETROFF</td>
<td>1935</td>
<td>192</td>
<td>33</td>
<td>Russia</td>
</tr>
<tr>
<td>NYSTROM</td>
<td>1922</td>
<td>59</td>
<td>47</td>
<td>Sweden</td>
</tr>
<tr>
<td>JACOBSSON</td>
<td>1948</td>
<td>277</td>
<td>45</td>
<td>Sweden</td>
</tr>
<tr>
<td>SCHINTZ and ZUPPINGER</td>
<td>1937</td>
<td>203</td>
<td>7</td>
<td>Switzerland</td>
</tr>
<tr>
<td>MARTIN, MUNSTER and SUGARBAKER</td>
<td>1940</td>
<td>556</td>
<td>13</td>
<td>United States</td>
</tr>
</tbody>
</table>

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**

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

Cade and Lee 61 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 Levy\textsuperscript{318} 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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{244} they observed that the highest incidence was in the age group of 40 to 45 years, while Rahausen and Sayago,\textsuperscript{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 Voutilaimen and Töövinen,\textsuperscript{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,\textsuperscript{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, Ariel\textsuperscript{3} claims that less than three per cent. of patients with lingual cancer are under 40 years of age. He and Tiecke\textsuperscript{361} 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 Bernier\textsuperscript{14} 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,\textsuperscript{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 Nathanson\textsuperscript{403} indicate this was 61 years, while Ueno et al.\textsuperscript{373} give the mean age of 53.1 years in a group of 103 patients investigated by them.
SITE OF OCCURRENCE

Shafer, Hine and Levy\textsuperscript{318} 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.

Tiecke\textsuperscript{361} 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,\textsuperscript{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,\textsuperscript{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,\textsuperscript{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 Baud\textsuperscript{34} 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.,\textsuperscript{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 Windeyer 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, and Colby, Kerr and Robinson 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, and Bernier. It is supported by the findings of Flamant et al., 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 Ariel 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,\textsuperscript{201} in a study of 556 cases, noted that about 50 per cent. were located along the edge of the tongue. They and Ariel\textsuperscript{3} 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.

Ariel\textsuperscript{3} 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-workers\textsuperscript{365} 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>
<thead>
<tr>
<th>Author</th>
<th>Year of Report</th>
<th>No. of Cases of Lingual Cancer</th>
<th>% of cases with history of syphilis or positive Wasserman reaction or both on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARY</td>
<td>1920</td>
<td>199</td>
<td>14</td>
</tr>
<tr>
<td>SCHREINER and BROWN</td>
<td>1926</td>
<td>127</td>
<td>48</td>
</tr>
<tr>
<td>LUND</td>
<td>1933</td>
<td>401</td>
<td>17</td>
</tr>
<tr>
<td>MARTIN, MUNSTER, and SUGARBAKER</td>
<td>1940</td>
<td>556</td>
<td>33</td>
</tr>
<tr>
<td>LEVIN, KRESS, and GOLDSTEIN</td>
<td>1942</td>
<td>146</td>
<td>14</td>
</tr>
<tr>
<td>SHARP and SPICKERMAN</td>
<td>1947</td>
<td>83</td>
<td>13</td>
</tr>
<tr>
<td>JACOBSSON</td>
<td>1948</td>
<td>277</td>
<td>14</td>
</tr>
<tr>
<td>GIBBEL, CROSS, and ARIEL</td>
<td>1949</td>
<td>230</td>
<td>22</td>
</tr>
</tbody>
</table>

Source: ARIEL

Wynder, Feldman and Bross, 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.

Martin\textsuperscript{180} 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 colleagues\textsuperscript{201} and Shafer, Hine and Levy\textsuperscript{318} are of the opinion that the relationship between syphilis and lingual cancer is purely from a local effect of syphilis rather than a generalized or systemic effect. Bernier\textsuperscript{16} 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 Sayago\textsuperscript{281} 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 Shroff\textsuperscript{244} 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, 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 Shroff 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, Rahausen and Sayago 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, Ariel 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 Levy\textsuperscript{318} indicate that leukoplakia is a common lesion of the tongue which has been observed many times to be associated with tongue cancer. Bourgoynne (quoted by Gardner, Schwartz and Pallen\textsuperscript{119}) states that lingual carcinoma is commonly preceded by leukoplakia, while Sarnat and Schour\textsuperscript{301} 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.

Ariel\textsuperscript{3} 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 associates\textsuperscript{365} 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 Sayago\textsuperscript{281} 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, \textsuperscript{244} in an analysis of 700 patients, report that leukoplakia co-existed with carcinoma in 32 per cent. of cases.

Shafer, Hine and Levy \textsuperscript{318} 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.\textsuperscript{3}

**SIGNS AND SYMPTOMS**

According to Ariel,\textsuperscript{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,\textsuperscript{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**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANT. $\tfrac{2}{3}$</td>
<td>902</td>
<td>696</td>
<td>266</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>POST. $\tfrac{1}{3}$</td>
<td>303</td>
<td>46</td>
<td>138</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1,205</td>
<td>742</td>
<td>404</td>
<td>115</td>
<td>152</td>
</tr>
</tbody>
</table>

Shafer, Hine and Levy 318 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, 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, 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, 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, in a study of 113 cases, observed that the average patient waited 6.3 months before consulting a physician, while Flamant et al. record an average delay of 4.6 months in the 904 cases investigated by him.

**CLINICAL APPEARANCE**

According to Martin, Munster and Sugarbaker, 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 hemorrhage, 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, and Ariel 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. Ariel adds that the lymphatics at the base of the tongue may occasionally be obstructed with cancer to produce a hideous macroglossia.

Baud 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.

Ariel 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 muscul-
ature, 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., 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 Lee 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 lymphoepithelioama 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 Rahausen and Sayago²⁸¹ in a review of 113 cases are as follows:
EPIDERMID 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 Lucas\textsuperscript{96} 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:

<table>
<thead>
<tr>
<th>Type of Tumour</th>
<th>No. Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQUAMOUS OR EPIDERMID CARCINOMA</td>
<td>1,505</td>
<td>96.9</td>
</tr>
<tr>
<td>ADENOCARCINOMA</td>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>MISCELLANEOUS</td>
<td>21</td>
<td>1.3</td>
</tr>
<tr>
<td>LYMPHOMA</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>LYMPHOANGIOSARCOMA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RHABDOMYOSARCOMA</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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 solanoid carcinomas, 2 basal cell carcinomas, and 2 recticular 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.

Ariel\textsuperscript{3} 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 |

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

Source: ARIEL\textsuperscript{3}

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 TUOVINEN$^{381}$ - 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 LUCAS$^{96}$ - Of 1,554 cases, 40 per cent. had positive regional node metastases clinically, and of these, 20 per cent. were bilateral.

MARCIAL$^{179}$ - 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 SHROFF$^{244}$ - 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 SAYAGO$^{281}$ - 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 SPICKERMAN$^{346}$ - 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 SUGARBAKER\textsuperscript{201} - 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 LEE\textsuperscript{61} - 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.

BERVEN\textsuperscript{35} - 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 Levy\textsuperscript{318} 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.