Oral Leukoplakia And Erythroplakia: A Review And Update

Jerry E. Bouquot, DDS, MSD

Soft tissue health in the oral cavity is essential for overall dental and medical health and a successful maintenance of any restoration. This article reviews the clinical, etiologic, and prognostic features of oral leukoplakia, the most common of all chronic mucosal lesions, affecting 3% of all adults. The newest definitions for leukoplakia, erythroplakia, and smokeless tobacco keratosis are offered, along with a rationale for predicting malignant transformation and for treatment planning of these most important precancers. The learning objective of this article is to update the information for the clinician for early diagnosis and treatment of these lesions.

One of the earliest associations between any benign lesion and the subsequent development of malignancy was made by Sir James Paget[1] in 1870, who suggested that oral "ichthyosis" (white keratotic plaque) was a significant precursor to lingual carcinoma. This association was independently advanced by Schwimmer,[2] who is usually credited with coining the

Dr. Bouquot is the Director of the Maxillofacial Center for Diagnostics and Research in Morgantown, West Virginia, and the Director of that center's International Biopsy Service and of the Roberts Research Foundation. He also is a Senior Visiting Scientist of the Mayo Clinic in Minnesota and a consultant to Pittsburgh Children's Hospital and the National Institutes of Health. Dr. Bouquot is on the National Board of Directors of the American Cancer Society, is one of the 32 professionals of the Research Committee of the American Cancer Society, reviewing and distributing $115 million in cancer research grants, and he is a reviewer for several journals, including JADA *and the* New England Journal of Medicine.

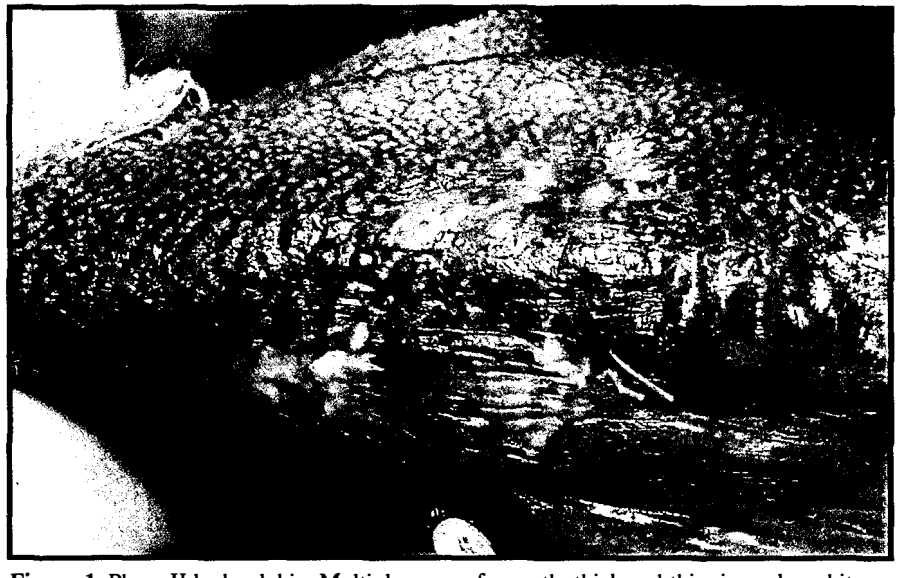

Figure 1. Phase II leukoplakia. Multiple areas of smooth, thick and thin, irregular white plaques of the lateral tongue.

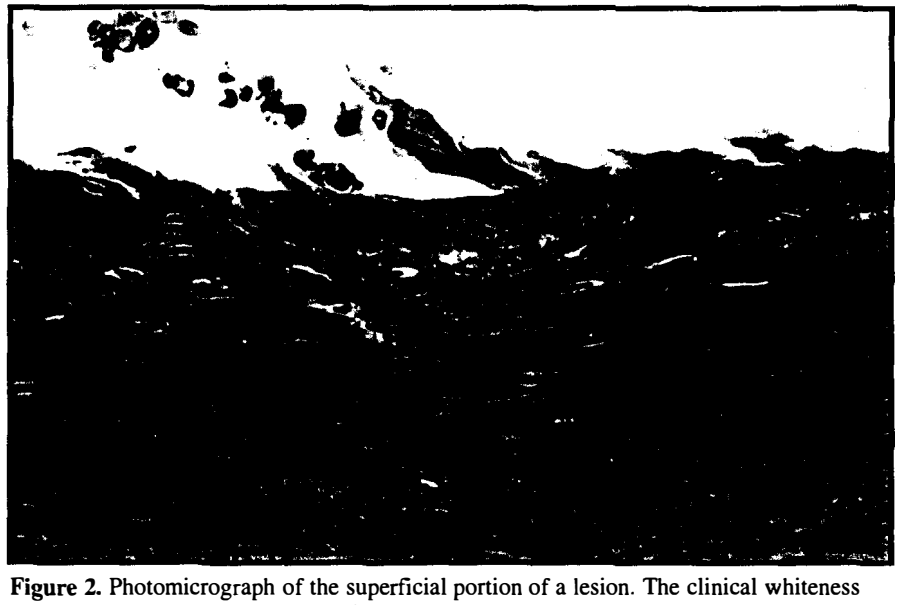

Figure 2. Photomicrograph of the superficial portion of a lesion. The clinical whiteness represents an increased thickness of the keratin layer.

term "leukoplakia." However, as late as the 1970s, there still was much controversy and confusion surrounding the concept.

Today, a variety of oral precancers are rather successfully evaluated and managed as a routine facet of oral health care. Because of the potentially fatal consequences of diagnostic mistakes relating to premalignant lesions, it is important for each clinician to remain knowledgeable and updated on the diagnostic and prognostic features of all premalignancies of the head and neck (H&N) area. The purpose of the present paper is to review two of these diseases — leukoplakia and erythroplakia — with additional commentary regarding smokeless tobacco keratosis.

DEFINITIONS

The World Health Organization (WHO) has provided simple but workable definitions of oral precancerous conditions and lesions.[3] The following variations of the WHO definitions are recommended for use with oral precancers and are used throughout this paper and a recent textbook of oral and maxillofacial pathology:[4]

It is especially important to remember that not all premalignancies eventually transform into cancer, as it was believed...

Precancerous Lesion (Precancer, Premalignancy) — A benign, morphologically altered tissue which has a greater than normal risk of containing a microscopic focus of cancer at diagnosis or of transforming into a malignancy after diagnosis.

Precancerous Condition — A disease or patient habit which does not necessarily alter the clinical appearance of local tissue but is known to have a greater than normal risk of precancer or

Figure 3. Phase I leukoplakia of border/lip mucosa with classic well-demarcated borders. (Courtesy Dr. William Young, Sydney, Australia.)

Figure 4. Extensive and thickened Phase III *candida leukoplakia*, which disappeared completely with topical antifungal therapy.

Figure 5. Chronic cheekbite can have many features of a Phase III or IV leukoplakia.

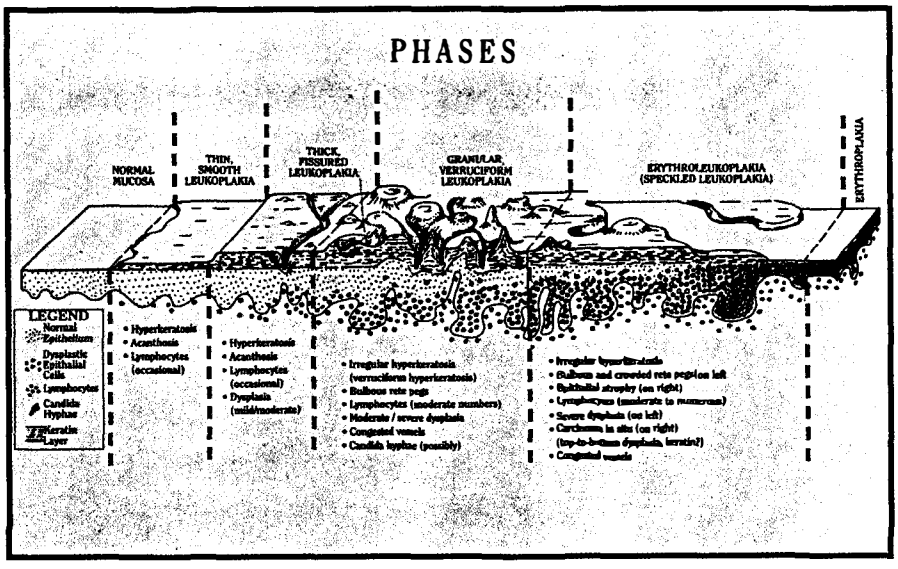

Figure 6. Diagrammatic representation of the four Phases. (Reprinted with permission, Bouquot & Whitaker, Quint Int 1994;25:133-140.)

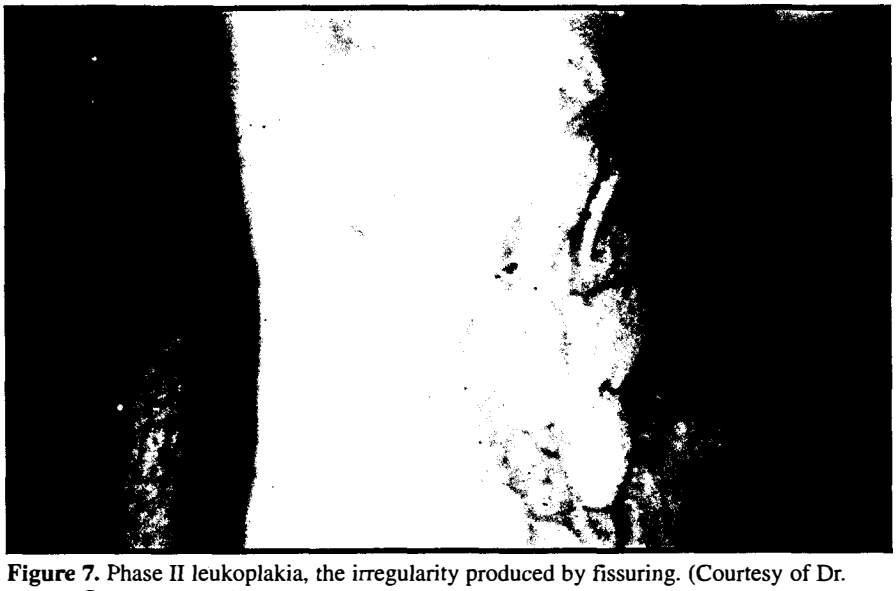

Figure 7. Phase II leukoplakia, the irregularity produced by fissuring. (Courtesy of Dr. Robert Gorlin, University of Minnesota.)

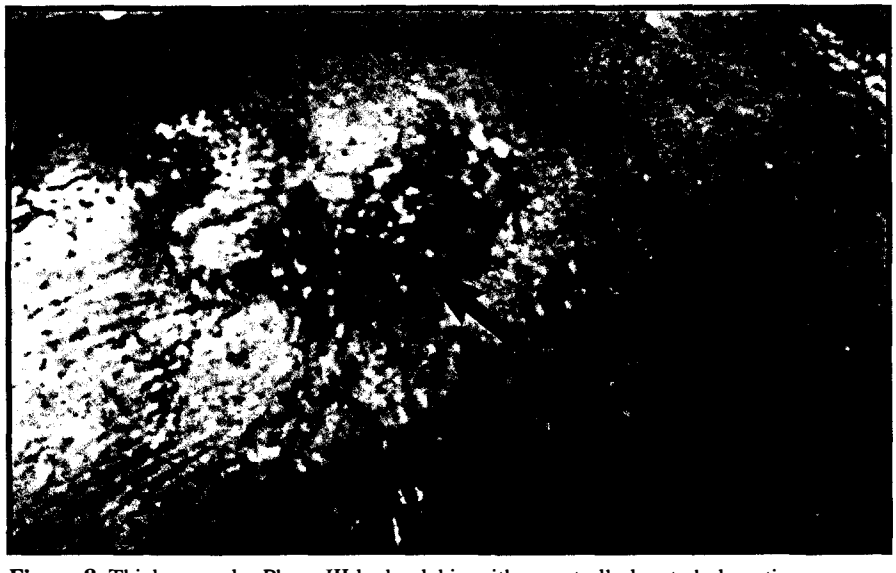

Figure 8. Thick, granular Phase III leukoplakia with a centrally located ulcerating squamous cell carcinoma already present.

Malignant Potential — The risk of cancer being present in a precancerous lesion or condition, either at the time of initial diagnosis or at a future date. The potential for mucosa without precancerous lesions or conditions is termed "normal."

Leukoplakia — A chronic white mucosal macule which cannot be scraped off, cannot be given another specific diagnostic name, and does not typically disappear with removal of known etiologic factors.

Erythroplakia — A chronic red mucosal macule which cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular, or inflammatory causes.

Smokeless Tobacco Keratosis — A chronic white or gray translucent mucosal macule, in an area of smokeless tobacco (ST) contact, which cannot be scraped off but disappears with cessation of the ST habit.

...oral leukoplakia is a diagnosis of exclusion...requiring the clinician...to be able to rule out all other white oral lesions.

It is especially important to remember that not all premalignancies eventually transform into cancer, as it was believed not too long ago; the transformation takes place only in a small proportion of cases. This means that the clinician may have to make some very real choices regarding the management of such lesions as leukoplakia, erythroplakia, smokeless tobacco keratosis, and lichen planus, and that the best choice may not always be a complete surgical removal but a good and rational follow-up protocol.

LEUKOPLAKIA – TERMINOLOGY AND DIAGNOSIS

Leukoplakia is a "white patch" of the oral mucosa (Figure 1), and, until recently, this term was also used for similar lesions of the larynx, vagina, uterine cervix, and bladder. It remains in use for head and neck sites, but its use for urogenital lesions has diminished. Cervical white-patch premalignancies are now being referred to as "human papilloma virus (HPV) lesions," "flat condylomas," or similar terms which reflect the newly discovered etiologic association with that virus. Several specific white keratoses have been taken off the term in the oral cavity as well, and a wide variety of diagnostic choices are now available for lesions which would have been called "leukoplakia" only 40 years ago (Table 1).

It must be emphasized that oral leukoplakia is a *diagnosis of exclusion* which requires the clinician to be so well acquainted with all white oral lesions as to be able to rule them out prior to using the term "leukoplakia" for a particular keratosis in a particular patient; the term itself is a clinical one. Even though biopsy and microscopic evaluation are frequently required in order to identify dysplastic or malignant cells, the presence of such cells does not alter the clinical diagnosis. If dysplastic cells are found under microscopic examination, the term is modified to "leukoplakia with dysplasia," "hyperkeratosis without dysplasia," or a similar phrase (Figure 2).

Leukoplakia affects approximately 3% of white adults and is the most common of all chronic mucosal diseases of the mouth.

TYPICAL CAUSES

Tobacco

While the exact etiology of oral leukoplakia still eludes us, tobacco smoking is by far the most broadly accepted factor.[5-10] More than 80% of leukoplakia patients are smokers,

Figure 9. Phase IV or erythroleukoplakia. Arrow indicates recent biopsy. (Courtesy Dr. Robert Graves, University of W.Va., Morgantown.)

Figure 10. Proliferative verrucous leukoplakia with multiple lesions and erythema. (Courtesy Dr. Jens Pindborg, Copenhagen, Denmark.)

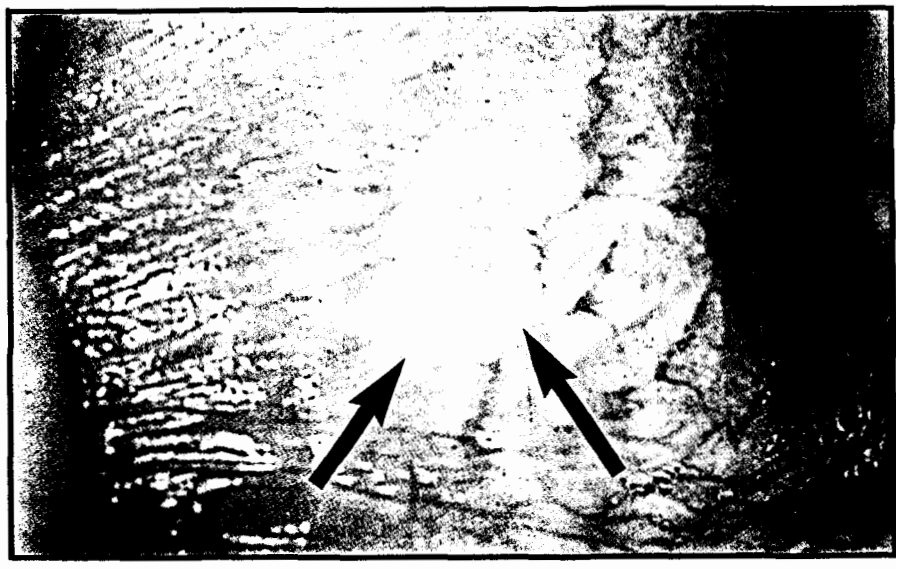

Figure 11. Smokeless tobacco keratosis occurs only in areas of direct tobacco contact.

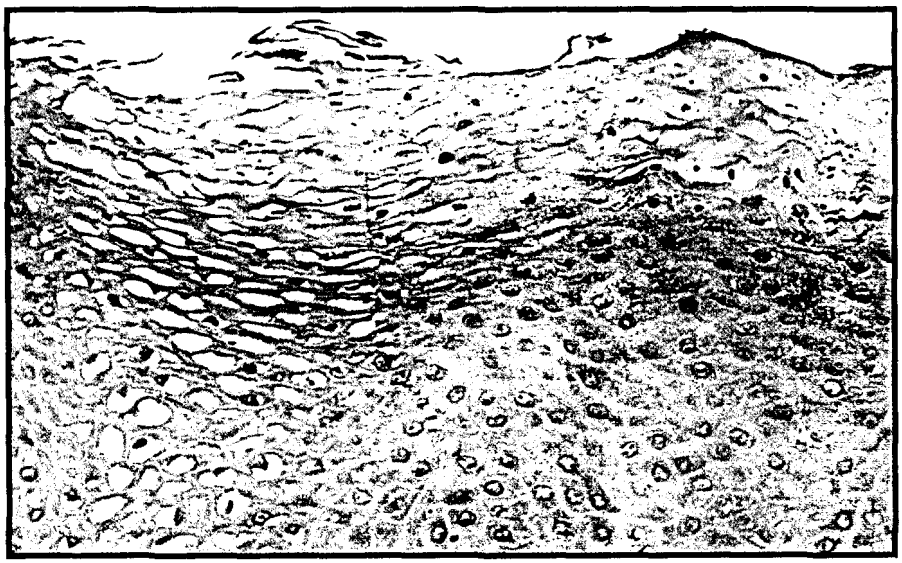

Figure 12. Photomicrograph of smokeless tobacco keratosis exhibits considerable "edema" within superficial keratinocytes.

Figure 13. Hairy leukoplakia occurs almost always on the lateral border of the tongue with vertical red groves between keratotic areas. (Courtesy Dr. S. Young, Oklahoma City, OK.)

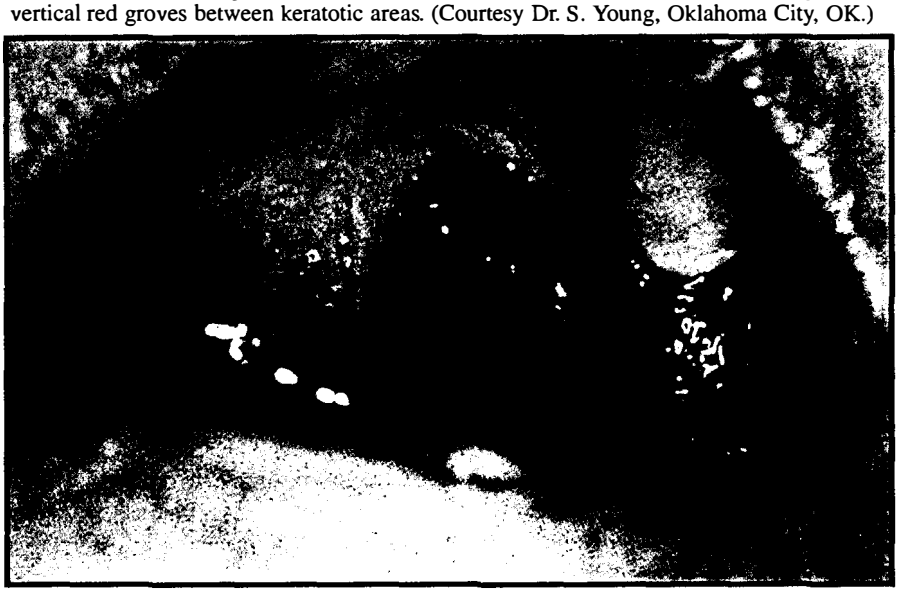

Figure 14. Erythroplakia of the lateral soft palate has well-demarcated borders and classic red appearance. (Courtesy Dr. James Weir, New Orleans, LA.)

nonsmoker ratio is 23 to 4.[6,11] Pipe smokers and heavy cigarette smokers have greater numbers of lesions and larger lesions than other smokers, especially after many years of tobacco abuse. Six to 12 months after smoking cessation, 60% of smoke-induced leukoplakias disappear.[11]

A dramatic example of positive correlation with tobacco was reported by an investigation among Indian villagers in the district of Bhaunagar, where the smoking of clay pipes is very popular among men and hardly ever done by women. The average annual leukoplakia incidence rate was 400 lesions/100,000 males versus 0 lesions/100,000 females.[12,13]

Ultraviolet Radiation

Ultraviolet radiation is another factor thought to cause leukoplakia of the lip vermilion, typically of the lower lip as a component of actinic cheilitis (farmer's lip, sailor's lip) (Figure 3). There is an extremely strong association between vermilion leukoplakia and vermilion carcinoma. In some rural populations, as many as two-thirds of all lip vermilion carcinomas have adjacent leukoplakia.[14] This is the strongest association for any cancer of the head and neck region.

Typical leukoplakia is 1.4 cm in diameter, and the patient has usually been aware of it for 2 years prior to professional diagnosis.

Microorganisms

Several microorganisms have been implicated in the etiology of leukoplakia.

Fungus *Candida albicans*. The fungus *Candida albicans* is found so often in severe, thickened cases that the terms *candida epithelial hyperplasia* and *candida leukoplakia* are commonly used (Figure 4).[6,15,16] It is not known whether this yeast produces dysplasia or secondarily infects previously altered epithelium, but the fungus is seldom found in mild cases,

and candida leukoplakias disappear or become altered to a lower phase level after topical antifungal therapy.

Papillomavirus. In the past, several viruses have been suggested as contributing to the production of oral leukoplakia, but only one, the human papillomavirus (HPV), appears to play a significant role.[17,18] Recently developed techniques have allowed investigators to identify this virus, especially subtypes 16 and 18, but the results have been equivocal. Polymerase chain reaction (PCR) has detected HPV in 3% to 40% of tested leukoplakias, but as much as 20% of normal oral epithelium contains the virus and, so far, such techniques have not been applied to large numbers of followed patients. Nor is it known whether HPV causes oral leukoplakia and oral cancers or merely enjoys living in tissues previously altered by some other unknown etiologic factor. Nevertheless, it is significant that HPV type 16 has been shown to induce dysplasia in squamous epithelium in an otherwise sterile in vitro environment.[19]

Chronic mechanical irritation is no longer considered important to the production of precancerous leukoplakia. Such obvious traumatic lesions as linea alba and chronic cheek bite (Figure 5) have never been reported to have transformed into malignancies. White lesions produced by mechanical irritation are best considered as frictional keratoses, which have no potential for malignant transformation.

TYPICAL PATIENT

Leukoplakia affects approximately 3% of white adults and is the most common of all chronic mucosal diseases of the mouth.[20-22] It represents 85% of all oral precancers and 80% of all precancers of the H&N mucosa.[6,20,23] Leukoplakia is much more prevalent among males than among females, especially in the oldest age groups.[5-7,20,24] Of all cases, 70% to 80% are males, although there is some indication that its frequency is increasing among females.[6,23,25] The prevalence increases to more than 8% in males aged over 75 years. The average age of affected persons is 60 years, similar to the oral cancer patients.

SUBTYPES OR PHASES

The typical leukoplakia is 1.4 cm in greatest diameter, and the patient has usually been aware of it for at least 2 years prior to professional diagnosis.[23] Because of its frequent changes over time and its varied clinical appearances, it is best to view leukoplakia not as a passive end-stage lesion (eg, as an irritation fibroma), but as an active and progressive disease, with any individual lesion having the potential to be found anywhere on a spectrum of 4 (or perhaps 5) clinical stages or phases (Figure 6).

Phase I

A lesion usually begins as a thin gray or white plaque, which is painless, nonhemorrhagic, and soft to palpation (nonindurated). The macule may have small surface wrinkles or fissures and is almost always well-demarcated from surrounding normal mucosa. Various names have been used for it at this stage, including thin smooth leukoplakia and preleukoplakia. To avoid confusion, Bouquot and Whitaker[25] have proposed calling it simply Phase I leukoplakia.

Phase II

With time, the mucosal plaque of a Phase I leukoplakia may disappear or acquire a thicker keratin layer and look more distinctly white (Figure 7). Most of the Phase II leukoplakias (smooth, thick, or homogenous leukoplakias) have smooth surfaces, but several present with an increased number and depth of surface fissures and other irregularities. Most cases remain in this phase indefinitely, some regress or disappear, and a few advance to more severe phases.

Phase III

In this phase, the lesions demonstrate more pronounced surface irregularities, usually of a papular or nodular nature, and are often referred to as granular, rough, or Occasionally the surface projections take on the appearance of pointed church spires or chevrons, in which case the term "verrucous leukoplakia" is applied. (It is not to be confused with the hairy leukoplakia, described on Page 15.) In Phase III, true leukoplakias may become dysplastic, even invasive, with no change in the clinical appearance of the surface, but change may occur in progression to a most severe level.

Phase IV

This phase is characterized by multiple circular or oval patches of nonblanching redness or erythema in scattered areas throughout the white patch (Figure 9). Such areas presumably represent sites at which the epithelial cells are too immature to produce keratin. Cellular immaturity can be interpreted as dysplasia, ie, the most likely sites for cancer development and the fruitful sites for biopsy material. The mixed red and white lesions are called erythro-, speckled, or nonhomogeneous leukoplakia.

A Possible Phase V

One rare and special form — proliferative verrucous leukoplakia (PVL) — has a strong tendency to be multiple, extensive, and rapidly progressive (Figure 10). It has such a high rate of malignant transformation that Hansen et al,[26] who originally described it, speculated that all cases may progress to carcinoma. While Bouquot and Whitaker[25] proposed only 4 phases, PVL might warrant being called a Phase IV plus, or Phase V leukoplakia.

TRANSFORMATION-INTO-CANCER POTENTIAL

Leukoplakia was initially suspected of being associated with oral carcinoma not only because the two lesions were frequently found adjacent to one another,[14] but also because many leukoplakic lesions exhibited atypical epithelial cells when viewed microscopically.[20,27,28] But the real proof of premalignancy can only be obtained from case-control and follow-up stud-

patients. Investigators now have reported the follow-up of more than 5,000 patients and have found malignant transformation rates, averaging approximately 4% to 6% and ranging from 1% to 28%.[5-7] The results of the largest of these follow-up investigations are summarized (Table 2). The malignant transformation potential of an individual leukoplakia depends on variables such as patient gender, habits, anatomic location of the lesion, and the exact clinical appearance of the lesion.

The risk of malignant transformation in Phase I and some Phase II lesions (Figure 6) may be so low that it is almost negligible. Conversely, the intermixed red and white patches of Phase IV carry an extremely high risk, which some studies have found to be as high as 30% to 40%.[7,28]

In addition to clinical appearance, other factors are important in predicting the malignant transformation potential. The presence of multiple lesions adds to the overall risk; a leukoplakia in a nonsmoker is apparently at a higher risk than the same lesion in a smoker. There is also evidence of higher risk when it occurs in females, although a U.S. study found that the lesions in white males had a considerably higher risk of malignant transformation than those in females.[20] Anatomic location appears to have some significance: Lesions of the oral floor and ventral tongue account for only 6% of all oral leukoplakias,[20,23] but as high as 40% of their biopsies show either severe epithelial dysplasia or actual carcinoma.[7,28] The figure has so alarmed some investigators that they have proposed a specific diagnostic terminology — sublingual keratosis.[5-7,28,29] Recent population studies, with reduced case-selection biases, have found the proportion to be considerably less than previously reported.

TREATMENT AND MANAGEMENT

Conservative surgical excision or removal by electrocautery, cryosurgery, or laser are the treatments of choice for oral leukoplakia, but not all lesions are candidates for complete removal.[5-7] While all but the most innocuous Phase I lesions should be biopsied at initial clinical diagnosis in order to establish the microscopic level of cellular maturity and atypia, not all lesions need to be removed. If no dysplasia is found in a Phase I or smooth Phase II lesion, careful and long-term follow-up is an acceptable management protocol.

Clinical evaluation every 6 months is recommended for untreated Phase I and II lesions; treated lesions should likewise be evaluated periodically for at least 3 years. Any recurring lesions should be either removed or followed indefinitely. Repeat biopsies should be performed for sites which progress into Phase III or higher. Complete removal should be effected for all Phase III or Phase IV leukoplakias and for any lesion diagnosed as moderate or severe epithelial dysplasia or carcinoma, with close clinical follow-up at 2- to 3-month intervals. No leukoplakia should be considered cured unless there has been no recurrence after treatment or after complete regression for at least 3 years.

TWO EXCEPTIONS TO BE NOTED

1. Smokeless Tobacco Keratosis

There are major differences between a true Phase I leukoplakia and the white patch produced by the chronic placement of chewing tobacco or snuff at a vestibular site.[9,10,30] The latter lesion, called snuff pouch or tobacco pouch in the past — and smokeless tobacco (ST) keratosis or spit tobacco keratosis today — is not a true leukoplakia but deserves some mention.

ST keratosis occurs only in areas of direct contact with snuff or chewing tobacco (Figure 11). It usually takes 5 to 10 years of tobacco use for a lesion to become apparent, but it may appear in less than a year. Typically, the keratosis has a semitranslucent appearance rather than a flat whiteness, and its microscopic appearance is different (Figure 12). The lesion is often fissured and poorly demarcated from surrounding mucosa, but otherwise it is quite uniform in consistency. It has a soft, velvety feel, and further palpation reveals a distinct "pouch," caused by flaccidity in the chronically stretched cheek muscles. Ulceration and pain are not associated with this lesion, but occasional erythema may be noted. Once it has developed, ST keratosis typically remains unchanged indefinitely, unless the daily ST contact time increases, in which case it will become thickened and appear distinctly white, leathery, or nodular — clinically indistinguishable from true leukoplakia. With abstinence from tobacco, ST keratosis is almost always completely reversible.

The malignancy potential of ST keratosis is 0.4% (versus 4% for leukoplakia).[30-32] If the ST keratosis lesion remains after tobacco cessation, the risk of malignancy increases, and the lesion should be considered to be true leukoplakia.

2. Hairy Leukoplakia

Hairy leukoplakia is a distinctive, rapid-onset keratosis with a papular or verruciform surface (Figure 13), but it is not a true leukoplakia and has no apparent malignant potential. It is essentially a keratin hyperplasia of the lateral tongue mucosa and is induced by the Epstein-Barr virus.[33] It is best termed oral HIV keratosis to eliminate confusion with true leukoplakias.

ERYTHROPLAKIA

Erythroplakia is the leukoplakia-like term used to describe clinically red and well-demarcated macules of the oral mucosa which cannot be attributed to traumatic or inflammatory factors (Figure 14). The typical patient is 57 years of age. Two-thirds of all oral cases are found in men (other than oral cases, the macules are found in uterine cervix). Etiologic factors for oral erythroplakia are essentially the same as those for oral cancer. Over 94% of affected patients smoke tobac-

co and more than 65% abuse alcohol. Microscopic examination reveals severe epithelial dysplasia or carcinoma in situ.[34-35] It may occur with or without leukoplakia and has been noted in a majority of early oral cancers.[36] While leukoplakias are diagnosed 77 times more often than erythoplakias,[23] the latter lesions are of far more serious consequence. Severe epithelial dysplasia has been shown to proceed to malignant transformation in at least one-third of all cases,[6] and carcinoma in situ is considered by many to be already a cancer, diagnosed in its preinvasive stage.[37] Therefore, it is best to consider carcinoma in situ to be a premalignancy. There is no information as to the typical length of time an oral carcinoma exists in situ before it begins to invade the underlying connective tissues, but three studies of laryngeal carcinoma have determined an invasive malignant transformation rate ranging from 33% to 90%.

All red macules of the oral mucosa which do not regress completely within 2 weeks after the removal of all local traumatic or inflammatory causes should be assumed to be erythroplakia, unless biopsy proves otherwise. More oral carcinomas are diagnosed in the earliest, preinvasive, red stage now than half-a-century ago.[38] Once dysplasia is confirmed by biopsy, all erythroplakias should be completely removed by the same techniques as used for leukoplakia, and long-term follow-up is just as crucial. After complete removal, 25% of intraoral carcinomas in situ will recur, 15% as the same lesion and 10% as invasive squamous cell carcinoma.

CONCLUSION

An effective soft tissue management is necessary for overall oral health and the long-term maintenance of any restoration. A review of the clinical, etiologic, and prognostic features of oral leukoplakia has been presented, along with the newest definitions, the various phases of the disease, treatment, and management. Erythroplakia, the more serious form of the lesions, has been discussed as well. The review should aid the clinician in an

TABLE 1

PARTIAL LISTING OF WHITE MUCOSAL LESIONS WHICH ONCE WOULD HAVE BEEN DIAGNOSED AS LEUKOPLAKIA

Disease Name	Precance
Smokeless tobacco keratosis (snuff pouch)	Yes *
Lichen planus	Yes *
Squamous papilloma	No
Leukoedema	No
White sponge nevus	No
Nicotine palatinus (smoker's palate)	No **
Frictional keratosis (oral "callous")	No
Chronic cheek bite	No

* Malignant potential is much lower than that of leukoplakia.
** Except in reverse smoking (smoking with lit end of cigarette within mou

TABLE 2

MALIGNANT TRANSFORMATION RATES (%) OF TH LARGEST LEUKOPLAKIA FOLLOW-UP STUDIES FROM EUROPE AND THE UNITED STATES

(Ranked by rates)

Authors	Country	Number of Patients	% Malignant Transformatio
Roed-Peterson, 1971	Denmark	331 *	3.6
Einhorn, Wersall, 1967	Denmark	782	4.0
Pindborg et al, 1968	Denmark	248	4.4
Kramer et al, 1970	England	187	4.8
Banoczy, 1977	Hungary	670	6.0
Bouquot et al, 1988	U.S.A.	463 **	10.3
Maerker, Burkhardt, 1978	Germany	200	12.0
Sturgis, Lund, 1934	U.S.A.	143	13.0
Silverman et al, 1984	U.S.A.	257	17.5
Leonardelli, Talamazzi, 1950	Italy	268	19.8
TOTAL		3,549	8.1 ***

* Probably includes same patient pool as Pindborg et al.
** Includes 13 cases from the pharynx.
*** Weighed for different sample sizes; many studies include a disproportional sampling of Phase II and IV lesions, the overall malignant transformation rate is usually considered to be 4% to 6% when all lesions are assessed.

NOTE: Used with permission, Ref. #35

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Answers To June/July 1994 Continuing Education Self-Test Exercises

[illegible]
[illegible] technique for obtaining consistent interproximal contacts in direct Class II composite restorations
By Charles E. Stone, DDS
Pages 15-20
1=d, 2=d, 3=a, 4=d, 5=a,
6=d, 7=d, 8=d, 9=d, 10=c

EXERCISE #61
Intra-radicular rehabilitation: A clinical approach
By George Freedman, DDS, Isaac M. Novak, DDS, Kenneth S. Serota, DDS, MMSc, and Gary D. Glassman, DDS
Pages 33-39
1=d, 2=b, 3=c, 4=c, 5=b,
6=b, 7=d, 8=c, 9=a, 10=b

EXERCISE #62
Achieving interdental integrity in resin-bonded posterior ceramic restorations
By William H. Liebenberg, BSc, BDS
Pages 43-51
1=d, 2=a, 3=c, 4=a, 5=d,
6=a, 7=c, 8=d, 9=b, 10=b

EXERCISE #63
The connective tissue graft with labial vestibular extension
By Peter O. Cabrera, DDS
Pages 57-63
1=b, 2=d, 3=a, 4=a, 5=c,
6=c, 7=a, 8=T, 9=d, 10=b