## TABLE 1.—Continued

| Study | Sample | Methods | Observations | Comments |
|---|---|---|---|---|
| Greer and Poulson, 1983 (cont.) | | • Clinical examination conducted of soft and hard oral tissues.<br>• Lesions graded according to a scale developed by Axéll et al. (1976) and modified by Greer and Poulson. | **Gingival and Periodontal**<br>• 26% of smokeless tobacco users had site-specific gingival recession.<br>• Users with lesions had longer use and higher daily exposure than users without lesions.<br>**Teeth**<br>• "... found no evidence of tobacco-associated dental caries."<br>• No evidence of occlusal or incisal abrasion.<br>• One case of cervical erosion. | • Smokeless tobacco-associated periodontal degeneration defined.<br>• Did not assess the interrelationship of smokeless tobacco, cigarettes, and alcohol. |
| Greer et al., 1986 | • 45 smokeless tobacco users (43 males and 2 females); 15 subjects in each group known as juveniles, young adults, and geriatric.<br>• Ages 13-74 years.<br>• Denver, Colorado. | • Cross-sectional design.<br>• Lesions graded by classification developed by Greer and Poulson, 1983.<br>• Examined only lesions classified according to scheme.<br>• Histomorphological methods used on tissue specimens.<br>• No statistical analysis conducted. | **Salivary Glands**<br>• Of 18 tissue samples with salivary glands, 4 demonstrated sialadenitis and degenerative changes.<br>• A routine pattern of chronic sialadenitis was not shown for any of the three age groups.<br>• Four patients (ages 21, 25, 50 and 66) showed either mild, moderate, or severe salivary gland fibrosis. | • Authors suggest that the degree of salivary gland fibrosis, degenerative change, and sialadenitis may be associated with tobacco brand instead of a generalized response caused by all tobacco. |

## TABLE 1.—Continued

| Study | Sample | Methods | Observations | Comments |
|---|---|---|---|---|
| Hirsch et al., 1982 | | | **Leukoplakia/ Mucosal Pathology** | |
| | • 50 male habitual snuff dippers.<br>• 41.3-year mean age (range 15-84 years).<br>• Sweden. | • Cross-sectional design.<br>• Subjects classified on a four-degree scale of lesion severity (developed by Axéll et al., 1976); biopsies were taken.<br>• Histomorphological and histochemical methods conducted on subjects' tissue specimens.<br>• Tobacco and alcohol use histories ascertained from a questionnaire. | • Interpretation of histomorphological and histochemical results demonstrated that the oral mucosal reaction to snuff-induced hyperplasia in the basal cell layers.<br>• Lethal damage was found in surface layers.<br>• Duration of use and daily exposure to smokeless tobacco were shown to affect the severity of the leukoplakia.<br>• Dysplasia could not be predicted by using suggested clinical degree of lesion classification. | • Dose considerations were made and confounding variables considered.<br>• Differences in brand of tobacco used were taken into account. |
| | | | **Salivary Glands** | |
| | • Tissue specimens from 74% of patients included salivary glands. | • Statistical analysis conducted: one-way analysis of variance and multiple comparisons using the Scheffe method. | • The salivary glands and excretory ducts showed degenerative changes of a more severe nature than found in the surface epithelium.<br>• 42% of salivary glands demonstrated sialadenitis and degenerative changes.<br>• Weak oxidative enzyme activities noted in acinic cells in salivary glands with sialadenitis and degenerative changes.<br>• Some signs of metabolic atypia noted.<br>• Markedly degenerative changes seen in salivary glands associated with the more severely, clinically classified lesions. | • Degenerative changes not specifically defined by authors.<br>• Authors state that variations in degenerative changes of salivary glands may be because of differences in brands of snuff and snuff-dipping habits. |

## TABLE 1.—Continued

| Study | Sample | Methods | Observations | Comments |
|---|---|---|---|---|
| Jungell and Malmström, 1985 | • 441 military recruits.<br>• Ages 17-19 years.<br>• Finland.<br>• 48 (11%) were snuff users.<br>• 18.9-year mean age (range 17-21 years). | • Cross-sectional design.<br>• Questionnaire administered to ascertain tobacco product use and drinking habits and frequency of dental care.<br>• Clinical examination conducted.<br>• Biopsies taken of 21 snuff users with lesions.<br>• Resting and stimulated (paraffin served as the stimulator) salivary excretions measured.<br>• Statistical analysis conducted: t-test.<br>• 10 nonusers of snuff also measured for salivary excretions. | **Salivary Glands**<br>• Resting salivary flow of snuff users was significantly higher than that of nonusers.<br>• Stimulated salivary flow was higher, but not significantly, among snuff users than among controls.<br>• There was no difference in buffering capacity between the two groups. | • Authors interpret difference in resting salivary flow to be a reaction to the presence of the local irritant snuff. |
| Modéer et al., 1980 | • 232 school children: 119 males, 113 females.<br>• 13.5 years mean age.<br>• 11% of males were regular snuff users.<br>• Sweden. | • Cross-sectional design.<br>• Interviewed about tobacco product use history and oral hygiene practices.<br>• Standardized dental indices used to measure changes in oral hygiene and periodontal conditions.<br>• Dental caries assessed clinically and radiographically.<br>• Statistical analyses conducted: cross tabulations, multiple regression, and student's t-test. | **Gingival and Periodontal**<br>• The use of snuff demonstrated a significant relation to gingivitis after controlling for plaque.<br>• Effects of snuff on the gingival tissue included both location of the snuff and as a predictor of gingivitis in general. | • Authors state snuff use may influence gingival tissue directly resulting in gingivitis.<br>• Examiners blind to responses from interview. |

## TABLE 1.—Continued

| Study | Sample | Methods | Observations | Comments |
|---|---|---|---|---|
| Offenbacher and Weathers, 1985 | • 565 males from 5 schools.<br>• 13.8-year mean age (range 10-17 years).<br>• 75 (13.3%) smokeless tobacco users.<br>• Georgia. | • Cross-sectional design.<br>• Questionnaire used to obtain history of tobacco product use, dental visits, and social history.<br>• Intraoral examination conducted using some standardized indices.<br>• Statistical analyses included: chi square, odds ratios, kappa coefficient calculations, and t-tests.<br>• Control group used. | **Leukoplakia/ Mucosal Pathology**<br>• Frequency of occurrence of soft tissue pathology was significantly elevated in users (primarily due to increased prevalence of white mucosal lesions).<br>• No attributable risk for mucosal pathology in smokeless tobacco users who were free of gingivitis.<br>**Gingival and Periodontal**<br>• No relationship between smokeless tobacco use and the prevalence of gingivitis.<br>• Prevalence of gingival recession significantly elevated in smokeless tobacco users.<br>• A significant attributable risk exists for gingival recession in smokeless tobacco users.<br>**Teeth**<br>• Smokeless tobacco users with gingivitis had significantly greater caries prevalence compared with nonusers without gingivitis.<br>• Prevalence of caries was significantly greater in users with gingivitis who used both snuff and chewing tobacco compared with nonusers with gingivitis or those who were gingivitis free. | • Soft tissue indices are not described.<br>• Method of selecting schools for subject ascertainment not described.<br>• Confounding variables considered.<br>• Smokeless tobacco use is viewed as a cofactor with the presence of gingivitis in promoting gingival recession.<br>• No clinical definitions provided for the assessment of gingivitis or gingival recession. |

**TABLE 1.—Continued**

| Study | Sample | Methods | Observations | Comments |
|---|---|---|---|---|
| Peacock et al., 1960 | | | **Leukoplakia/ Mucosal Pathology** | |
| | • 1,338 employees of local textile mill.<br>• North Carolina. | • Cross-sectional design.<br>• Interviewed about tobacco product use and given an oral examination. | • Highly significant relationships between chronic snuff and tobacco use and oral leukoplakia development found for all age groups and for both sexes. | • Examiners blind to interview responses.<br>• 90% of employees had either poorly fitting complete dentures or only few and carious teeth.<br>• Many employees have had the habit since they were 3 years old. |
| Poulson et al., 1984 | | | **Leukoplakia/ Mucosal Pathology** | |
| | • 445 subjects: 52% females, 47% males.<br>• 56 (12.6%) smokeless tobacco users (all males).<br>• 16.7-year mean age (range 14-19 years).<br>• Rural Colorado. | • Cross-sectional design.<br>• Questionnaire administered (same as one used in Greer and Poulson, 1983).<br>• Clinical examination conducted of oral hard and soft tissues.<br>• Lesions graded by classification developed by Greer and Poulson, 1983. | • Of 56 smokeless tobacco users, 35 (63%) had lesions of the hard or soft tissues.<br>• 33 (58.9%) smokeless tobacco users had mucosal alterations.<br>• Mucosal lesions were found in area of quid placement.<br>• Duration of use and length of daily exposure were factors in the development of lesions.<br>• Multiple lesions in the same subject reported. | • Examiners blind to responses on questionnaire.<br>• Definitions of clinical states provided.<br>• Comparisons to nonusers not reported.<br>• A history of confounding variables obtained. Effects of variables not addressed statistically. |
| | | | **Gingival and Periodontal** | |
| | | | • Of 56 smokeless tobacco users, 15 (27%) had site-specific gingival recession: 2 users had periodontal lesions only; 13 had both mucosal lesions and periodontal destruction. | • Periodontal degeneration defined.<br>• Effects of confounding variables not addressed statistically. |

## TABLE 2.—Summary of Selected Case Reports

| Study | Country | Number of Users | Age | Product Used | Duration of Use | Findings |
|---|---|---|---|---|---|---|
| Archard and Tarpley, 1972 | USA | 3 | 31<br>42<br>60 | Snuff<br>Snuff<br>Snuff | 11 years<br>20 years<br>50 years | A homogeneous eosinophilic submucosal deposit above the minor salivary glands did not initiate an inflammatory response nor support the possibility that the deposits were amyloid. |
| Christen, Armstrong, and McDaniel, 1979 | USA | 1 | 36 | Snuff | 13 years | Gingival recession, clinical leukoplakia, periodontal bone loss, and tooth abrasion found where tobacco was habitually placed. |
| Christen, McDaniel, and Doran, 1979 | USA | 14 | 18-22 | Snuff, chewing tobacco | 6 months to 9 years | 8/14 with clinically detectable gingival recession; 9/14 with clinical leukoplakia; 11/14 with erythematous soft tissue changes where tobacco or snuff was habitually held. |
| Frithiof et al., 1983 | Sweden | 21 | 31-79 | Snuff | 10-60 years | 21/21 with snuff-induced lesions localized to area where snuff was held; 2/21 with observable gingival retraction. |
| Hoge and Kirkham, 1983 | USA | 1 | 20 | Snuff | 1 year | Gingival recession and hyperkeratosis found where tobacco was habitually placed. |
| Pindborg and Poulson, 1962 | Denmark | 7 | Not reported | Snuff | 20-30 years | 4/7 had whitish mucous membrane with a delicately folded appearance at site of snuff placement. |
| Pindborg and Renstrup, 1963 | Denmark | 12 | 39-83 | Snuff | 20-50 years | 12/12 with mucous membrane that was "whitish, sometimes yellowish-brown, dry appearance with a very delicately folded or finely grooved surface." |
| Zitterbart, Marlin, and Christen, 1983 | USA | 1 | 36 | Chewing tobacco | 24 years | Gingival recession, "smokeless tobacco-users lesion," and abraded occlusal surfaces of posterior teeth found where tobacco was habitually placed. |

# THE EFFECTS OF SMOKELESS TOBACCO USE ON ORAL LEUKOPLAKIA/MUCOSAL PATHOLOGY AND THE TRANSFORMATION OF ORAL SOFT TISSUES

## Oral Leukoplakia/Mucosal Pathology

### Background and Definitions

Various oral soft tissue effects of smokeless tobacco use have been reported in the literature. These effects include oral leukoplakia/mucosal pathology. The actual terms used and the definitions employed to describe these conditions vary widely from study to study (table 3). The World Health Organization (WHO) defines oral leukoplakia as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease *(1)*. The mucosal pathology that is found in smokeless tobacco users also has been referred to as hyperkeratosis, an oral mucosal lesion that exhibits an abnormal whitish (keratinized) appearance clinically. The authors' terms are employed when a specific study's findings are described. However, in the discussion portion of the report, the general terms of oral leukoplakia/mucosal pathology are used.

The association between smokeless tobacco use and oral leukoplakia/mucosal pathology has been moderately studied. The WHO has stated that tobacco is an etiologic agent for the formation of oral leukoplakia *(1)*. This association was reaffirmed at an International Seminar on Oral Leukoplakia and Associated Lesions Related to Tobacco Habits *(2)*. In a review of the effects of tobacco habits other than smoking, the use of smokeless tobacco/snuff was associated with the presence of leukoplakia *(3)*.

### Studies in the United States

Six studies have addressed the prevalence of oral leukoplakia/mucosal pathology in smokeless tobacco/snuff users *(4-9)*. In two of these studies, blindness of the examiners toward the tobacco habits of the subjects was maintained, and oral tissue findings in smokeless tobacco users and nonusers were compared *(7,9)*. Three of these studies investigated adults *(4-6)* and three investigated adolescents *(7,9)*. In addition, several case reports have described oral leukoplakia/mucosal pathology findings in smokeless tobacco users *(10-13)*. Highlights of these studies and reports are summarized below.

Offenbacher and Weathers investigated the oral tissue effects of smokeless tobacco use in adolescent males from the greater metropolitan area of Atlanta, Georgia *(9)*. They used oral examinations and self-administered questionnaires on tobacco use. Of the 565 males who were examined, 75 (13.3 percent) used smokeless tobacco. The difference in the prevalence of mucosal pathology in smokeless tobacco users (22.7 percent) was statistically significant compared with that of nonusers (4.7 percent); however, the authors did not provide specific diagnostic

**TABLE 3.—Variations in Terms Used and Definitions Provided for Leukoplakia/Mucosal Pathology Associated With Smokeless Tobacco Use by Studies Cited**

| Study | Term(s) Used | Definition(s) Provided | Comments |
|---|---|---|---|
| Axéll, 1976 | Snuff-dipper's lesion. | A four-category classification scheme based on tissue color, wrinkling, and thickening was used. | The authors believe that this is a well-defined irritation that excludes it from the diagnosis of leukoplakia. |
| Christen, Armstrong, and McDaniel, 1979 | Clinical leukoplakia. | "Implies only the clinical feature of a white patch or plaque on the oral mucosa which will not rub off and which cannot be characterized clinically or histologically as any other specific disease." | The authors cite the WHO 1978 and Waldron and Shafer 1975 references *(1,47)*. |
| Christen, McDaniel, and Doran, 1979 | Leukoplakia. | "Implies only the clinical feature of a white plaque on the mucosa . . ." | The authors cite the Waldron and Shafer 1960 reference *(48)*. |
| Frithiof et al., 1983 | Snuff-induced lesion. | "Tissue changes in the oral mucosa" that are due to snuff use. | The authors cite the WHO 1978 reference for the definition of leukoplakia and state that "since the snuff-induced lesion, with its typical clinical pattern and its specific etiology, obviously constitutes a definite diagnostic entity, the term 'leukoplakia' is avoided . . ." |
| Greer and Poulson, 1983 | Oral mucosal lesions (alterations) associated with the use of smokeless tobacco. | These lesions were defined by a modification of a clinical grading method developed by Axéll et al., 1976. | In addition, lesions were classified by their texture, contour, and color. |
| Hirsch, Heyden, and Thilander, 1982 | Snuff-induced lesions. | These lesions were defined by the grading method developed by Axéll et al., 1976. | — |

**TABLE 3.—Continued**

| Study | Term(s) Used | Definition(s) Provided | Comments |
|---|---|---|---|
| Hoge and Kirkham, 1983 | Hyper-keratotic-appearing tissue. | No definition is provided, although the authors discuss the "formation of a hyperkeratotic zone in the region of the 'snuff pouch' where the tobacco is habitually held." | The authors cite the Shafer, Hine, and Levy 1969 reference *(49)*. |
| Moore, Bissinger, and Proehl, 1952 | Oral leukoplakia. | No definition provided. | — |
| Offenbacher and Weathers, 1985 | Mucosal pathology, soft tissue pathology. | No definitions provided. | The pathological findings identified by the investigators included morsicatio, ulcer, keratosis/leukoplakia, vesiculobullous, petechiae, abscess, erythema, mucocele, and pericoronitis. |
| Peacock, Greenberg, and Brawley, 1960 | Leukoplakia. | "A pearly white plaque on the mucous membrane which could not be scraped off with a tongue blade." | — |
| Pindborg and Poulson, 1962 | Leukoplakia. | No definition provided. | The investigators described the mucous membrane as having a slightly whitish, delicately folded appearance. |
| Pindborg and Renstrup, 1963 | Snuff-induced leukoplakia. | No definition provided. | The investigators described the leukoplakias as "slightly whitish, sometimes yellowish-brown, dry appearance with a very delicately folded or finely grooved surface." |
| Poulson, Lindenmuth, and Greer, 1984 | Oral mucosal lesions (alterations) associated with the use of smokeless tobacco. | The clinical appearance of these lesions was defined by a grading method developed by Greer and Poulson, 1983. | Alterations in texture, color, and contour of the mucosal lesions also were identified. |
| Zitterbart, Marlin, and Christen, 1983 | Generalized smokeless tobacco-users lesion. | No definition provided. | The lesion was described clinically as "peculiarly wrinkled and thickened." |

criteria in this assessment. The range of mucosal pathologic findings included such conditions as morsicatio (cheek biter's lesion), ulcer, keratosis/leukoplakia, vesiculobullous, petechiae, abscess, erythema, mucocele, and pericoronitis. Although 50 percent of the smokeless tobacco users with mucosal pathology had keratosis/leukoplakia compared with 3.8 percent of the nonusers with mucosal pathology, the authors did not identify the locations of the mucosal pathologies.

Peacock, Greenberg, and Brawley reported a significant relationship between chronic tobacco use and the presence of oral leukoplakia* in a study of 1,388 textile mill workers in North Carolina *(5)*. The 362 employees who reported using smokeless tobacco had a significantly higher prevalence of leukoplakia (34 percent) than did the 457 nonusers (7.4 percent). In addition, the authors noted a direct leukoplakia and age effect.

In a study conducted in Denver, Colorado, Greer and Poulson examined 1,119 teenagers in grades 9 to 12 to assess the relationship between oral tissue alterations and the use of smokeless tobacco *(7)*. Smokeless tobacco was used by 117 (10.5 percent) of these teenagers. Of these, 42.7 percent had oral mucosal lesions† in the area of tobacco placement. Forty-six percent of the teenagers with mucosal lesions also had concomitant periodontal tissue degeneration.‡

Poulson, Lindenmuth, and Greer examined a sample of 445 teenagers in five rural Colorado towns to assess the relationship betwen oral tissue alterations and smokeless tobacco use *(8)*. Smokeless tobacco was used by 56 (12.6 percent) of the teenagers. Of these, 58.9 percent had oral mucosal lesions in the area of habitual tobacco placement. Concomitant periodontal degeneration was noted in 39.4 percent of those with oral mucosal lesions.

Contrasting the results of rural versus urban adolescent smokeless tobacco users, Poulson, Lindenmuth, and Greer suggested that the duration of use may be critical in the development of "oral lesions" *(8)*.§ Those adolescents with oral lesions used smokeless tobacco longer (an average of 3.3 years in the rural and urban groups) than those without lesions in both the rural and urban groups (2.3 years and 2.2 years, respectively). In addition, the authors noted similar effects of different levels of smokeless tobacco use in daily exposure. Users with oral lesions were exposed 205 minutes per day in the rural group and 177 minutes per day in the urban group compared with users with no oral lesions (110 minutes and 53 minutes, respectively). Also, more than twice

---

* Leukoplakia was defined as a "pearly white plaque on the mucous membrane which could not be scraped off with a tongue blade."

† The authors used a modification of the classification method that was developed by Axéll et al. that identifies the oral mucosal lesions according to color, wrinkling, and thickening *(14)*.

‡ The authors define this degeneration as "site-specific gingival recession with apical migration of the gingiva to or beyond the cementoenamel junction, with or without clinical evidence of inflammation."

§ The term "oral lesions" used here includes periodontal tissue degeneration and oral mucosal lesions.

as many marked oral mucosal lesions were identified in the rural population as in the urban population.

Smith et al. examined a population of 15,500 snuff users by cytological, histological, and visual means *(6)*. Of these users, 1,751 (11.3 percent) demonstrated oral mucous membrane changes. Although no definitions were provided, these changes were described as "cloudy or gray glistening" areas having "wrinkled appearance(s)" and presenting "white or red granular appearance(s)." The authors reported that when snuff was withdrawn, the tissue returned to normal appearance.

Moore, Bissinger, and Proehl investigated the relationship between tobacco use and oral cancer in male patients age 50 years and older who attended the General Tumor Clinic in Minneapolis, Minnesota *(4)*. The authors noted that a significant number of the patients who manifested oral leukoplakia (18 of 23—78.3 percent) used smokeless tobacco. A tobacco user in this study was defined as a person who used the tobacco product for 20 or more years. Apparently, some of these 23 patients were also pipe, cigar, or cigarette smokers, although the exact number was not specified. The authors indicated that the most severe patches of leukoplakia were seen in patients who chewed "strong" tobacco and over a longer duration (no quantification reported). In most instances in which patients had stopped using smokeless tobacco, leukoplakia disappeared.

Several case reports (table 2) have described oral leukoplakia/mucosal pathology at the site of smokeless tobacco/snuff placement *(10-13)*. These cases represent males of various ages with differing years of smokeless tobacco/snuff use. Hoge and Kirkham reported that in one patient, withdrawal of snuff resulted in a reversal of the hyperkeratotic lesions *(12)*.

**Studies in Scandinavia**

Studies of smokeless tobacco from Scandinavia have investigated the prevalence of oral leukoplakia/mucosal pathology in users *(15-19)*.

Axéll found 1,444 smokeless tobacco users (predominantly men) in the 20,333 Swedes who were examined for soft tissue lesions *(17)*. Of these users, 116 (8 percent) had "snuff-dipper's lesion" (see table 3 for definitions). The prevalence of oral leukoplakia among the total study population was 3.6 percent.

Hirsch, Heyden, and Thilander *(18)* graded oral mucosal lesions on an established four-point scale *(14)* and correlated these findings with the snuff habits in 50 Swedes ages 15 to 84 years who used snuff routinely. Younger patients were found to have lower degrees of pathologic changes, while a significant predominance of older patients was noted with higher degrees. The authors reported that patients with oral mucosal lesions of the highest degree had used snuff an average of 34.7 years compared with the 9.2- to 13.6-year average for patients with lower degrees of pathologic changes. They also noted that patients with high degrees of pathologic changes dipped twice as long per day (an

average of 10.1 and 10.6 hours per day) as patients with lower degrees of pathologic changes (5.2 and 6.5 hours per day, respectively). Although these patients reported multiple tobacco habits, the authors stated that no differences in clinical grading were found between patients who used snuff only and those who used snuff and other tobacco products.

In addition, several case reports have described oral leukoplakia/mucosal pathology (table 2). In Sweden, Frithiof et al. examined 21 male snuff users ages 31 to 79 years *(19)*. All had snuff-induced lesions that were localized to the area in the oral cavity where the tobacco was held. Similarly, leukoplakia lesions were found at the site of snuff placement in all 12 male users of snuff ages 39 to 83 years in a study in Denmark *(15)*. In this latter study, 3 weeks after one of the patients discontinued snuff use, the clinical appearance of the mucous membrane had returned to normal. In another report, four of seven Danish male users of snuff exhibited leukoplakia at the site of snuff placement *(16)*.

**Discussion**

The studies from the United States and Scandinavia demonstrate that oral leukoplakia/mucosal pathology is associated with smokeless tobacco/snuff use. In two studies, a higher prevalence of oral leukoplakia/mucosal pathology was found in users compared with nonusers of smokeless tobacco—22.7 percent compared with 4.7 percent *(9)* and 34.0 percent compared with 7.4 percent *(5)*. In all of these studies, between 8 and 59 percent of smokeless tobacco/snuff users were found to have oral leukoplakia/mucosal pathology.

It appears that the oral leukoplakia/mucosal pathology noted in smokeless tobacco/snuff users is found commonly at the habitual site of tobacco/snuff placement. Using a similar grading classification for snuff-induced lesions *(7,14)*, all of the mucosal pathology that was noted in four studies was at the site of habitual tobacco placement *(7,8,17,18)*. Similarly, the majority of the oral leukoplakia/mucosal pathology that was described in the case reports was found where the tobacco/snuff was usually placed.

The duration of use (in years) and daily exposure (in hours or minutes) to smokeless tobacco appear to be critical in the development and severity of oral leukoplakia/mucosal pathology. Three studies using similar approaches to the definition of oral leukoplakia/mucosal pathology and to the measurement of exposure noted this effect *(7,8,18)*.

Only two studies were designed to study the concomitant findings of oral leukoplakia/mucosal pathology and other tissue changes. The authors reported that 39.4 *(8)* and 46.0 *(7)* percent, respectively, of smokeless tobacco users with oral leukoplakia/mucosal pathology also had periodontal tissue degeneration (gingival recession). These oral soft tissue changes also were found at the site of habitual tobacco placement.

In several studies where individuals had stopped smokeless tobacco use, the oral leukoplakia/mucosal pathology disappeared *(4,6,12,15)*.

## Transformation of Oral Soft Tissues

### Background and Definitions

The previous section that discussed smokeless tobacco-induced leukoplakia noted that clinically observable changes in soft tissue morphology do occur as a result of smokeless tobacco use. Smokeless tobacco-associated lesions that have been traditionally classified as leukoplakias (white lesions) offer varying clinical degrees of differentiation and may persist or progress with continued smokeless tobacco use. Additionally, some leukoplakias have been observed to resolve clinically upon the cessation of smokeless tobacco use. This section of the report addresses the transformation of oral soft tissues. It discusses the potential for smokeless tobacco-induced lesions to regress, persist, or continue to progress to lesions with higher malignant potential or to malignancy.

There are varying clinical and histologic definitions in the scientific literature related to tobacco-induced changes (transformation) of oral soft tissues. The following definitions represent those most frequently encountered. It will be noted when significant variation of these definitions occurs in studies cited:

- Oral leukoplakia—a white patch or plaque that cannot be characterized clinically or pathologically as any other disease *(1)*.
- Snuff dipper's leukoplakia—a leukoplakia associated with the use of smokeless tobacco. These are further characterized as to differing morphologic forms.
- Erythroplakia—a lesion present as a bright red patch or plaque that cannot be characterized clinically or pathologically as any other condition, such as carcinoma or infection.
- Precancerous condition—a generalized state that is associated with an increased risk of cancer based on epidemiologic or histologic evidence.
- Precancerous lesion—a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart.
- Acanthosis—an increased thickness of the spinous cell layer of the epithelium.
- Hyperkeratosis—an increased thickness of the keratinized layer of the epithelium.
- Hyperparakeratosis—an increased thickness of a normally parakeratotic layer of the epithelium, i.e., surface cells with retained nuclei.
- Hyperorthokeratosis—an incrased thickness of a normally keratotic layer of the epithelium, i.e., surface cells without retained nuclei.

- Chevron keratinization—a keratinization pattern typified by vertical streaks of parakeratinization that extend to the epithelial surface and create surface irregularities by extensions of the outer surface layer.
- Dysplasia—abnormal tissue development characterized by varying numbers and degrees of morphologic cell changes that reflect grades of severity.
- Dysplastic changes include the following:
  - Pleomorphism in the size and shape of cells and their nuclei.
  - Abnormal numbers of cells undergoing mitotic activity (discrepancy in maturation).
  - Atypical mitotic cells.
  - Cytoplasmic atypicalities (altered nuclear to cytoplasmic ratio).
  - Hyperchromasia.
  - Irregular nuclear borders.
  - Basal cell hyperplasia.
  - Loss of polarity.
- Carcinoma in situ—a significant number of dysplastic epithelial cell changes that extend from the basal layer to the surface layer without violation of the basement membrane.
- Verrucous carcinoma—a clinically verruciform cancer of epithelial tissue that tends to be slowly and locally invasive with a metastasis and mortality potential that is lower than classic squamous cell carcinomas. The cells are well differentiated.
- Squamous cell carcinoma—a cancer of the stratified squamous epithelium that has varying clinical appearances, is invasive, extends beyond the basement membrane, and has a great potential for metastasis.

Evidence of the relationship between smokeless tobacco use and the transformation of oral soft tissues is represented by the following:

1. Clinical reports describing tobacco habits of persons with graded oral lesions.
2. Followup (cohort) studies of tissue changes, including transformation to malignancy, among patients with leukoplakia.
3. Case-control studies or case series of oral cancer describing concomitant leukoplakia.

A review of the evidence in each of these study areas follows:

### Clinical Reports of Oral Lesions in Association With Smokeless Tobacco Use

Hirsch, Heyden, and Thilander *(18)* graded oral snuff-induced mucosal lesions in 50 patients on a four-point scale according to criteria developed by Axéll *(14)*:

- Degree 1: A superficial lesion with a color similar to the surrounding mucosa, slight wrinkling, and no obvious thickening.
- Degree 2: A superficial whitish or yellowish lesion with wrinkling and no obvious thickening.
- Degree 3: A whitish-yellowish to brown lesion with wrinkling, intervening furrows of normal mucosal color, and obvious thickening.
- Degree 4: A marked white-yellowish to brown lesion with heavy wrinkling, intervening deep and reddened furrows, and heavy thickening.

Snuff habits and drinking habits of the patients were obtained from questionnaires. Patients in the degree 4 category had been snuff dippers significantly longer than the rest of the patients. Also, patients in degrees 3 and 4 dipped approximately twice as long per day as did patients in degrees 1 and 2. The daily exposure to snuff was significantly longer in degree 4 (10.6 hours) than in degrees 1 (5.2 hours) and 2 (6.5 hours). When total exposure was compared between the four clinical groups taking into account hours of use per day as well as years of use, significant differences were found.

In this study, no significant differences could be found with regard to clinical grading and histological appearances between patients with multiple habits (snuff, smoking, and drinking) and those who only used snuff. The four clinical degrees of lesions exhibited an age-dependent effect with younger patients usually found in clinical degrees 1, 2, and 3 and a significant predominance of older patients noted in degree 4. Degree 4 lesions included an increased number of mitotic figures, edema, and slight to moderate inflammation compared with the other three degrees. Eighteen percent of the patients exhibited slight epithelial dysplasia, and lesions with slight epithelial dysplasia were found in all categories. Patients in the dysplastic group had been snuff dippers longer on average (23.9 years) as compared with those without dysplasia (19.5 years). No case of moderate or severe dysplasia was noted. (The authors referenced the WHO Collaborating Center for Oral Precancerous Lesions as the definition for dysplasia *(1).*)

Axéll, Mörnstad, and Sundström obtained biopsies of the oral mucosal lesions of 114 male dippers ages 20 to 88 years from a sample of 1,200 Swedish snuff dippers *(14).* Clinically, lesions were graded (degrees 1 through 4) based on color and morphology. Lesions of higher clinical degrees were associated with greater daily exposure to snuff in terms of hours and grams of exposure. All but one of the biopsies showed increased epithelial thickness. The outer layers appeared vacuolated with occasional remnants of cell nuclei. Lesions in degrees 3 and 4 had more pronounced surface layers. Acanthosis was evident in all of the clinical groups. None of the biopsies showed changes that were interpreted as cellular atypia or epithelial dysplasia. The cessation of

snuff dipping for a few days was reported to result in clinical regression of the lesions with loss of the vacuolated layer.

Greer et al. reviewed clinically and histologically examined smokeless tobacco-induced leukoplakias from 45 patients ages 13 to 74 years *(20)*, following criteria that were previously established by Greer and Poulson *(7)* as adapted from Axéll. The vast majority of the mucosal lesions were corrugated, white, and raised. No evaluations for an interrelationship between smokeless tobacco use, smoking, and alcohol use and clinical or histologic tissue changes were attempted. Histologic examinations for specific changes were reported. Dark cell keratinocytes characterized by a strong affinity for basic dyes and by electron density of their cytoplasm and nucleus and suggested as dedifferentiated precursors of a neoplastic keratinocyte were found in 17 of 45 cases. However, their presence was unrelated to the clinical degree of the lesion. While they have also been observed in leukoplakias that are associated with smoking (or other causes), the control group of nontobacco-induced hyperkeratoses demonstrated dark cell keratinocytes in only 3 of 45 cases. Chevron keratinization of the epithelial layer representing altered cellular maturation was present in 42 of 45 smokeless tobacco-induced leukoplakias but in only 4 of 45 control leukoplakia cases. Koilocytotic changes appearing as vacuolated epithelial cells that may obscure the cytoplasm or appear with pyknotic nuclei, which are often associated with inclusion of viral particles in epithelial cells, were present in 27 of 45 smokeless tobacco-induced leukoplakias. In the entire sample of 45 cases, only 1 case of dysplasia (described as occurring in a long-term smokeless tobacco user) was identified. Three of the following characteristics had to be present for a lesion to be characterized as dysplastic:

- Loss of cellular polarity.
- Basal cell hyperplasia.
- Altered nuclear/cytoplasmic ratios.
- Anaplasia.
- Dyskeratosis.
- Atypical mitoses.

Because the dysplasia case also involved the use of alcohol and smoking, it is not possible to attribute its appearance solely to smokeless tobacco use.

In a study of 21 Finnish military recruits ages 17 to 21 years, mucosal lesions corresponded to the site of snuff placement and included the alveolar and labial mucosa to varying degrees *(21)*. The duration and intensity of snuff use for this specific group could not be determined from the study. Epithelial hyperplasia and acanthosis were universally found under the light microscope. Hyperorthokeratinization was noted in 12 cases, hyperparakeratinization in 9 cases, and Chevron-type keratiniza-

tion in 1 case. One case of mild epithelial dysplasia was noted that included atypical and increased mitoses and loss of basal cell polarity. The authors concluded that this suggests a positive relation between snuff dipping and malignant changes.

Van Wyk biopsied 25 snuff-induced lesions from Bantu smokeless tobacco users whose lesions had existed from a few weeks to 40 years *(22)*. Comparison biopsies were also taken from healthy parts of the mucosa in the users, from healthy mucosa in nonusers, and from other white lesions and squamous carcinomas. From the biopsies obtained from snuff users, 18 cases of acanthosis, 23 cases of parakeratosis, 5 cases of keratosis, and 4 cases with numerous mitotic figures, pleomorphism, hyperchromatism, and an irregular basal cell layer were noted. Additionally, 11 showed a disrupted appearance of the basement membrane. Those not associated with inflammation were considered possibly to be premalignant. Epithelium featuring these characteristics has been referred to by some as "disquiet epithelium." Contrarily, the author stated that "the impression is gained that no relationship exists between oral malignancy and the use of snuff." This was based on the widespread use of snuff but the occurrence of only one case of alveolar or sulcular cancer (not in a snuff user) in the hospital during this study.

Several investigators have described connective tissue changes in snuff-induced lesions. A hyalinized, eosinophilic material that occurs well below the epithelium and around the minor salivary glands or in a plane that is generally parallel to the epithelial surface has been reported by Pindborg et al. *(16)*, Archard et al. *(23)*, Axéll et al. *(14)*, and Greer et al. *(20)*. The exact nature of and underlying explanation for the finding are not clear. Additionally, the role of such a histologic finding in the development or progression of premalignant or malignant lesions has not been identified.

**Cohort Studies**

Several investigations have followed persons with oral lesions for subsequent health outcomes. Smith reported the 10-year followup results on a group of patients with smokeless tobacco-induced leukoplakias *(24)*. In the original study, oral cytologies were performed on 1,751 patients presenting with leukoplakias out of 15,500 snuff users *(6)*. Results of the oral cytology examination consistently indicated only benign hyperkeratoses.* Biopsies were made of 157 leukoplakic lesions. However, no objective criteria for lesions selected for biopsy were offered. None of the biopsies showed changes consistent with dyskeratosis or malignancy. These patients were followed with repeat cytology smears for 5.5 years. No additional significant mucosal changes were

* The use of oral cytology for detecting dysplastic changes in leukoplakic lesions is less than satisfactory because of a high rate of false negative findings. The hyperkeratinized nature of leukoplakic lesions renders them resistant to the oral cytology scraping technique. Cellular changes in deeper layers of the epithelium would thus likely be missed *(25)*.

reported. In a subsequent 4.5-year followup (10 years total followup), periodic biopsies were done on 128 of the 157 patients who had originally received biopsies *(24)*. The authors reported no dyskeratosis or carcinomas in the followup study. The method of followup was not specified. Significant numbers of patients were lost, and the clinical and histologic diagnostic criteria were not fully described.

A prospective study of oral cancer among persons with oral leukoplakia or other possible precancerous lesions was conducted in the Ernakulum district, Kerala State, India, as part of a 10-year followup to a much larger study of 50,915 adults in 5 rural districts of India *(26)*. Among those individuals who had been diagnosed as having a leukoplakia during the original survey, there was a malignant transformation rate of 9.7/1,000 per year for those who only chewed tobacco. For those who both smoked and chewed, the rate was 5/1,000 per year, while no malignancies were reported for individuals with or without tobacco habits who had not had a previous oral lesion. The transformation rates among those with lesions were much higher than rates reported in the United States or European studies. While these results are not directly comparable to United States or European studies since the tobacco chewed in India is a variable mixture of betel leaf, areca nut, slake lime, and coarse tobacco, they suggest that the persons with leukoplakia are at increased risk of oral cancer. Specific clinical morphotypes of leukoplakia demonstrated varying potentials for malignant transformation: homogeneous, 2.27 percent; speckled, 21.4 percent; and ulcerated, zero percent.

In a small study of English coal miners, 8 of 22 patients with leukoplakia who chewed tobacco were followed for 5 years *(27)*. Five of the eight cases showed no advance in the lesions, and two showed regression. The author does not specify whether these were clinical or histologic determinations or whether the smokeless tobacco habit persisted in all cases. One lesion that had been regarded as benign showed some hyperorthokeratosis and acanthosis of the epithelium but with no more than "minor epithelial atypia." The clinical appearance of this lesion was reported to have regressed initially over an intermediate 2-year period despite continuance of the habit of tobacco chewing and smoking. Subsequent followup over a 2-year period indicated that the lesion had progressed to an exophytic squamous cell carcinoma. The site of the lesion was where the patient had held tobacco for 30 years. While the malignant transformation rate in the group of chewing tobacco-associated leukoplakias was 12.5 percent, the small numbers and high dropout rate limit the significance of the finding. Of significance was the unpredictable course of the malignant lesion, initially regressing and then transforming into a squamous cell carcinoma.

In a Danish study, 32 patients with snuff-induced leukoplakias from a group of 450 patients with leukoplakia were observed for a median time of 4.1 years *(28)*. Each patient had also used alcohol, with 17 per-

cent claiming daily use. Thirty-three biopsies demonstrated hyperplastic epithelium with hyperparakeratosis in 87 percent of the cases; half showed vacuolated cells. One initial case of epithelial dysplasia was found, and one carcinoma was found to develop from a nondyskeratotic leukoplakia over the followup period. This represents a rate of premalignant or malignant transformation of 6.2 percent for either dysplasia or carcinoma. In comparing the rate of development of dysplasia and carcinoma from snuff-induced leukoplakias to nonsnuff-induced leukoplakias, the authors found no statistically significant differences. However, the rate of transformation in both groups was higher than would be expected in individuals without leukoplakic mucosa.

In an earlier report on a small sample of 12 white male snuff-using leukoplakia patients (use from 20 to 50 years), Pindborg and Renstrup did not find any malignant transformation *(15)*. Biopsies were taken from sites where the snuff was held. All 12 showed unkeratinized hyperplasia of the epithelium with a few deep streaks of parakeratosis and downgrowth and broadening of the rete pegs with the outer layers of cells being vacuolated and large. The authors state that snuff-induced leukoplakias are easily reversible. Based on the limited size of this sample, definitive conclusions could not be made.

**Oral Lesions Concomitant With Oral Cancer**

Three hundred and thirty-three patients with cancers of the buccal cavity and pharynx from the Robert Winship Memorial Clinic in Atlanta, Georgia, were compared with three control groups: a group with diseases of the mouth other than cancer or with no diseases; a group with cancer of sites other than the mouth, pharynx, or larynx; and a group without cancer and whose mouths were not examined—see chapter 2 *(29)*. The authors, citing leukoplakia as a precancerous condition, found leukoplakias "more commonly in women with low grade squamous carcinomas arising in the mouth and with multiple cancers. Snuff dipping was frequently associated with leukoplakia and low grade cancer arising in the mouth."

In a case-control study in Minnesota of cancers of the alveolar ridge, floor of the mouth, and buccal mucosa, it was noted that leukoplakias and cancers of the mouth were related to the use of snuff or chewing tobacco *(4)*. The most severe leukoplakias were reported among those who used "strong snuff" (no definition was provided) and held the quid at the same site for many years. Patients who quit using smokeless tobacco reportedly had leukoplakias disappear in most instances. A number of patients had multiple primary carcinomas that were also specific to the site of quid placement. Cancer lesions were described as having developed slowly over a period of several years, although no evidence of periodic clinical or histologic assessment was provided.

McGuirt reported on 76 oral cancer patients, most with carcinomas of the alveolar ridge or buccal mucosa, identified from the tumor registry

at the North Carolina Baptist Hospital who had a documented history of heavy smokeless tobacco use *(30)*. Fifty-seven of these patients used snuff and reported no cigarette, pipe smoking, or alcohol habits. The range of use was from 10 to 75 years. Leukoplakias had previously been excised in 13.9 percent of the cases, and 47 percent had associated leukoplakias at the time of surgery. The author cited "panmucosal insult" from smokeless tobacco use as the cause of multiple lesions and recurrences—a type of field cancerization.

From histologic evaluations of oral tissue among 23 Swedish patients with anterior oral vestibular cancer who were snuff users, leukoplakic lesions were noted outside the snuff-associated tumor in 5 *(31)*. Leukoplakia and multiple carcinomas occurred together with the snuff-associated lesion in three cases. Eleven of nineteen cases assessed for presence of candida were positive. The temporal relationship between candida and carcinoma was not ascertainable, nor was the potential etiologic role of candida.

Rosenfeld and Callaway examined data from records at Vanderbilt University Hospital, Nashville General Hospital, and the office of Rosenfeld for cases of squamous cell carcinoma arising in the mucous membrane of the anterior two-thirds of the tongue, the floor of the mouth, the gingiva, and the buccal area *(32)*. A total of 525 cases were examined in users and nonusers of smokeless tobacco—300 occurred on the gingiva and buccal areas. Among women with cancer of the buccal or gingival area, 90 percent had a history of snuff use. While no periodic quantitative or qualitative assessment of the natural history of the cancers is provided, the authors do offer the following clinical impression of snuff-induced lesions in their study:

> These carcinomas arising in the inner cheek and gingiva frequently start as leukoplakia. Progressive thickening, cornification, and eventual cauliflower-like ulcerations ensue. All stages in the progressive disease may be seen in microscopic sections from a mere slight increase in the keratin layer, through carcinoma in situ to invasive malignancy.

Twenty-five cases of histologically confirmed buccal gingival cancer in female snuff users were identified at the University of Arkansas Medical Center from 1950 to 1959 *(33)*. Eleven cases occurred at buccal sites, 10 gingival, and 4 buccal and gingival. The patients (ages 44 to 84 years—mean 67.5) had a smokeless tobacco habit between 20 and 50 years. The lesions corresponded to the site of habitual tobacco placement. Leukoplakia was a concomitant lesion and had been present for many years. Repeat biopsies of lesions were made over long periods in some of the patients. Leukoplakic lesions from other parts of the mouth often showed atypia. An evolution from leukoplakia to pseudoepitheliomatous hyperplasia to early squamous cell carcinoma was found.

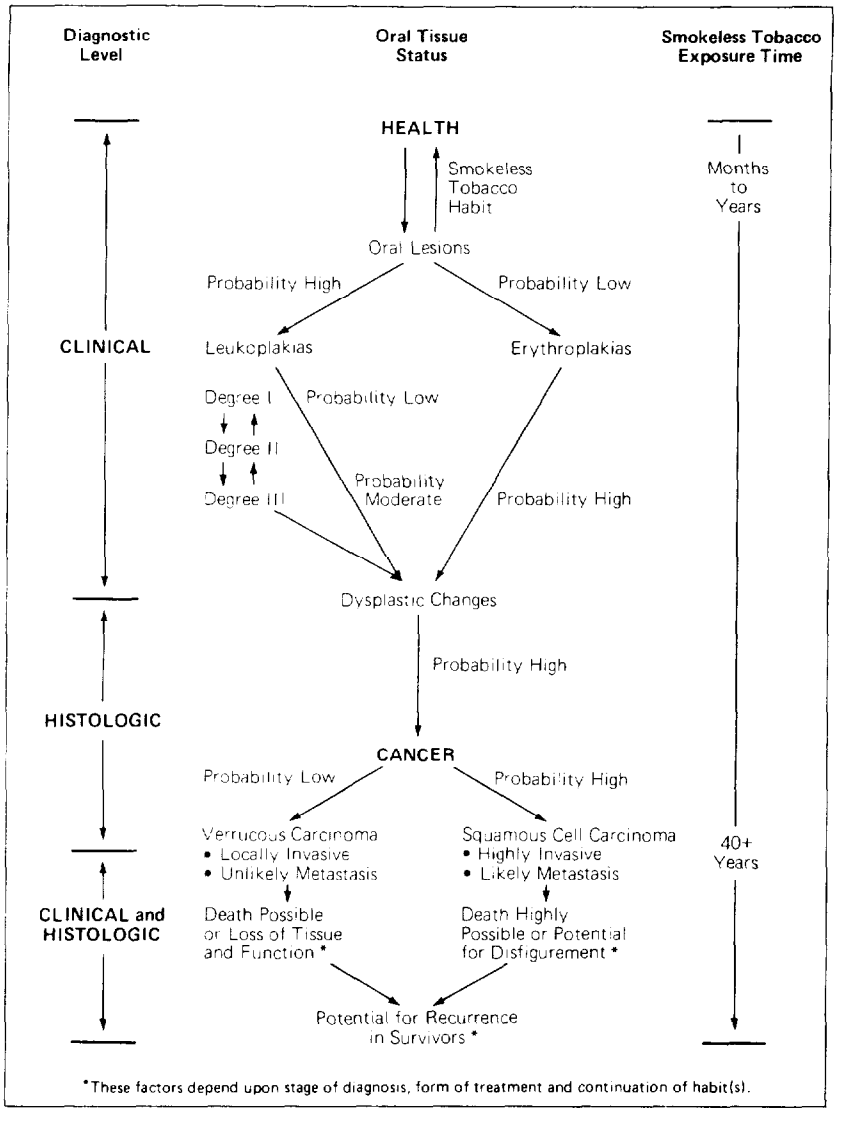
**Discussion**

In characterizing the role of smokeless tobacco use in the clinical and histologic course of oral lesions, there are several problems. First, oral leukoplakia should be considered a dynamic changing lesion of the oral mucosa *(34)*. Lesions retain the potential to resolve, remain static, or progress depending on a variety of factors that may be either exogenous (e.g., smokeless tobacco use) or endogenous (e.g., natural tissue defenses and repair potential). To achieve comparability of results among investigators, a standard system for gauging epithelial dysplasia is needed. Patients then could be followed prospectively to quantify the incidence of dysplastic change, incidence of transformation from a dysplastic state to a cancerous state, or in some cases transformation from an apparently benign to a cancerous state. But ethical considerations do not allow lesions to be monitored continuously from benign states to moderate and severe dysplasias and carcinoma in situ.

The next best alternative would be to provide estimates of risk for malignant transformation based on empirical and clinical observations or at least to quantify descriptively the association that smokeless tobacco-induced lesions have with other lesions or other potential etiologic factors. The body of literature on smokeless tobacco-induced lesions and their potential for malignant transformation allows for the development of a conceptual model of the natural history of smokeless tobacco-induced lesions (figure 1). This model is a composite of various prospective, retrospective, cross-sectional, and case studies that relate to smokeless tobacco-induced lesions. It depicts progressive changes that may occur in some individuals who are habitual users of smokeless tobacco and potential outcomes that could include death or disfigurement for some individuals who use smokeless tobacco for several decades. The data are clear that habitual smokeless tobacco use can produce mucosal lesions (see leukoplakia discussion). It is also clear that where groups of patients with smokeless tobacco-induced leukoplakias have been followed for several years, cases of cancer have been identified. Finally, when considering studies of oral cancers in habitual smokeless tobacco users, there appears to be a consistent finding of leukoplakias either having been previously excised in the area of habitual tobacco placement or being found concurrently with and in proximity to oral cancers.

In comparing studies on the transformation potential of smokeless tobacco-induced leukoplakias, it is found that different criteria have been used by various investigators in defining dysplastic changes. The number and nature of criteria that are considered and that are considered adequate to classify a case as dysplastic are not consistent. Additionally, the degree of agreement on diagnosis based on histology and clinical history between individuals has been shown to be quite variable. Pindborg, Reibel, and Holmstrup tested the degree to which a group of

**FIGURE 1.—A Conceptual Natural History of Oral Mucosal Changes Associated With the Use of Smokeless Tobacco**



oral pathologists could agree on diagnoses where nine cases of epithelial dysplasia, carcinoma in situ, or initial squamous cell carcinoma were examined *(35)*. Color photomicrographs and information on the topography of the biopsy were presented. The authors' diagnoses were based on the criteria that are described in the report from the WHO International Collaborating Center for Oral Precancerous Lesions *(1)*. The degree of agreement with the authors' diagnoses for the nine cases ranged between 10 and 78 percent. This could partially explain the range in prevalence and incidence of malignant transformation that is reported by various investigators.

Other contributing factors in comparing studies could include different population groups in terms of age and gender and other confounding variables (e.g., smoking, alcohol use, and type of smokeless tobacco product used). Each of these limitations is suggestive of the type of research that is needed.

## THE EFFECTS OF SMOKELESS TOBACCO USE ON THE GINGIVA, PERIODONTAL TISSUE, AND SALIVARY GLANDS

### Background and Definitions

Reports of gingivitis, gingival recession, and degenerative salivary gland changes associated with smokeless tobacco use are contained in the literature. As with the previous section on oral leukoplakia, the terms used and the definitions employed to describe gingivitis and gingival recession vary widely from study to study. Table 4 displays the variations found in the literature. As each study is described in the following narrative, the authors' terms are employed. However, in the discussion portion of this report, the general terms of gingivitis and gingival recession are used. General definitions for these terms and for sialadenitis follow:

- Gingivitis—This condition refers to clinically detectable acute or chronic inflammation, either local or general, of the gingiva.
- Gingival recession—In general, this condition describes the apical migration of the gingiva with or without clinical evidence of inflammation.
- Sialadenitis—Inflammation of the salivary glands.

### Gingival and Periodontal Tissue

Studies that assess the relationship between smokeless tobacco use and gingival and periodontal tissue effects are limited. The literature consists of several cross-sectional studies in teenagers and a few case reports.

**TABLE 4.—Variations in Terms Used and Definitions Provided for Gingivitis and Gingival Recession by Studies Cited**

| Study | Term(s) Used | Definition(s) Provided | Comments |
|---|---|---|---|
| Christen, Armstrong, and McDaniel, 1979 | Gingival recession, periodontal pocket, and loss of alveolar bone. | No definitions provided. | The tissue changes were described in general by the authors. |
| Christen, McDaniel, and Doran, 1979 | Clinically detectable gingival recession. | No definitions provided. | — |
| Greer and Poulson, 1983 | Tobacco-associated periodontal degeneration and periodontal lesions. | "Defined as site-specific *gingival recession* with apical migration of the gingiva to or beyond the cementoenamel junction, with or without clinical evidence of inflammation." | — |
| Hoge and Kirkham, 1983 | Gingival recession. | No definition provided. | The authors defined the recession as having "exposed approximately 5 mm of labial root surface" and having destroyed the "entire functioning border of keratinized gingiva." |
| Modéer, Lavstedt, and Ahlund, 1980 | Gingivitis/gingival inflammation. | Estimated on the basis of the gingival index of Löe and Silness, 1963 *(50)*. | — |
| Offenbacher and Weathers, 1985 | Gingivitis. | No definition provided. | — |
| | Gingival recession. | No definition provided. | The gingival recession was "considered slight to moderate, ranging in 1-4 mm apical migration when present." |
| Poulson, Lindenmuth, and Greer, 1984 | Tobacco-associated periodontal degeneration (other terms include "periodontal deterioration," and "localized periodontal degeneration associated with the site of tobacco placement"). | "Defined as site-specific *gingival recession* with apical migration of the gingiva to or beyond the cementoenamel junction, with or without clinical evidence of inflammation." | — |
| Zitterbart, Marlin, and Christen, 1983 | Gingivitis. | No definition provided. | — |
| | Gingival recession. | No definition provided. | The clinical findings were described for each tooth site involved. |

**Studies in the United States**

Three cross-sectional studies have investigated the relationship of gingival and periodontal tissue changes and smokeless tobacco use in teenagers in the United States *(7-9)*. Offenbacher and Weathers examined the effects of smokeless tobacco use on mucosal pathology, on the presence of gingivitis and gingival recession, and on dental caries status (discussed in next section) *(9)*. Of the 75 smokeless tobacco users, the authors noted 72 percent with gingivitis and 60 percent with gingival recession. In those with gingival recession, 6.6 percent presented with recession in direct juxtaposition to the location of the tobacco placement. The authors did not describe how many users of smokeless tobacco had demonstrated combinations of these oral conditions. Also, no specific clinical definitions were given for the assessment of gingivitis or gingival recession, although the latter findings were described as "slight to moderate, ranging from 1 to 4 mm apical migration of gingival tissue." The higher prevalence of gingival recession among smokeless tobacco users (60 percent) as compared with that found in nonusers (14.1 percent) was found to be statistically significant. There were no statistically significant differences in gingivitis prevalence between smokeless tobacco users (72 percent) and nonusers (77.1 percent).

Of 117 adolescent smokeless tobacco users in Denver, Colorado, Greer and Poulson noted that 25.6 percent had tobacco-associated periodontal degeneration *(7)*. As noted earlier, this condition was defined as "site-specific gingival recession with apical migration of the gingiva to or beyond the cementoenamel junction, with or without clinical evidence of inflammation." Concomitant mucosal lesions were noted in 76.6 percent of those who had periodontal degeneration (gingival recession).

In a study of rural Colorado teenagers, Poulson, Lindenmuth, and Greer *(8)* described 26.8 percent of 56 smokeless tobacco users with periodontal degeneration (gingival recession) as defined by Greer and Poulson *(7)*. Eighty-seven percent of these had concomitant mucosal lesions.

Several case reports (table 2) describe the occurrence of gingival recession and periodontal tissue destruction in individual smokeless tobacco/snuff users *(10-13)*. The patients in these case reports were males who ranged in age from 18 to 36 years with varying duration of the smokeless tobacco/snuff habit ranging from 1 to 24 years. Although not universally found, gingival recession was usually noted, and the majority of patients presented with recession that was specific to the site where the tobacco/snuff was habitually placed.

Periodontal bone loss at the site of snuff placement was described in another patient who used snuff for 13 years *(10)*. In one patient, 3 weeks after cessation of snuff use, there was no regeneration of the lost gingival tissue, although, as noted earlier, the hyperkeratotic areas had disappeared *(12)*.