

The Cytology of Benign Oral Lesions

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Exfoliative cytology is now a well established technique to facilitate and accelerate clinical and histopathologic recognition of oral carcinoma. In large, advanced, obviously malignant oral lesions, cytology has no effective role; however, in small, early, malignant oral lesions, cytologic scrapings have proved most useful in aiding detection.^{17, 19} This is because early oral carcinomas often do not have any consistent diagnostic features and are innocuous in appearance. At the same time many benign lesions, which frequently are observed in the mouth, display extremely variable features. Therefore, many benign lesions will be initially examined with cytologic scrapings while attempting to differentiate benign from malignant neoplasia, as well as to help guide clinical management which may involve medication, removing irritants, incisional or excisional biopsy, referral or other modes of care. The purpose of this paper is to illustrate and discuss when exfoliative cytology may be useful in aiding identification of a benign lesion or condition and to point out some of the cytologic atypias which are observed.

NORMAL ORAL HISTOLOGY AND CYTOLOGY

The entire oral cavity is lined by stratified squamous epithelium which varies in surface cornification and specialized functions from area to area (Fig. 1). Exfoliated surface cells from the soft palate, ventral tongue and floor of the mouth demonstrate almost complete cytoplasmic basophilia and have nuclei which are spherical and contain evenly stippled chromatin patterns. Each nucleus is centrally located in abundant surrounding cytoplasm. On the other hand, cells shed from the surface of the mucosa of the hard palate, gingiva and dorsal tongue display varying degrees of nuclear pyknosis, anucleosis and cytoplasmic acidophilia. The labial and buccal mucosal surface cells are intermediate in maturity. Although cytoplasmic acidophilia in oral surface cells has traditionally been associated with keratin formation, caution should be taken in making this assumption. The lack of consistent findings between kerato-hyaline granules and cytoplasmic

fibrils with acidophilia and basophilia indicates that another biochemical feature may also be responsible for variations in staining reaction.

Estrogen Effects

The majority of reports^{20, 24, 27, 24, 8} indicate that the menstrual cycle exerts no cyclical estrogenic influence on oral epithelial cornification. A repeat study now in progress at our institution once again confirms these findings. Buccal scrapings from 24

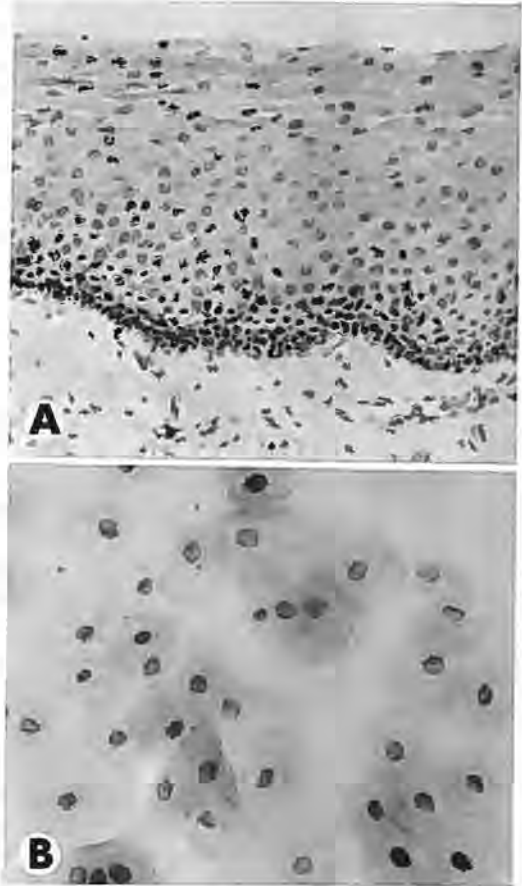


FIG. 1. A. Stratified squamous epithelium obtained from human buccal mucosa. B. Cells scraped from the buccal mucosal surface prior to biopsy of specimen in A.

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FIG. 2. Cytologic scraping from an intact mucosal surface of the floor of the mouth following irradiation. Note nuclear enlargement and multinucleation (A), parabasal-like cell (B), polymorphonuclear leucocytes (C), and a cell-within-a cell configuration (D).

women, aged 19 to 37, were obtained twice weekly through 2 complete cycles. Although there were variations between subjects, there were no consistent altered cornification patterns within an individual. Also, estrogen administration to postmenopausal women with osteoporosis has shown no interval changes in oral scrapings or biopsies, while vaginal smears from this group have reflected the expected estrogenic effect.

Chromosomal Sex

Buccal scrapings obtained to observe the presence of Barr bodies, the heterochromatic X-chromosomes seen adjacent to the nuclear border during interphase, have been useful in determining chromosomal sex.^{11,7} While these bodies may be seen in approximately 20 to 80 percent of cells from females, they are observed in less than 5 percent of cells from male oral scrapings.

Anemias

Reports by Farrant,⁴ Boen¹ and Monto⁹ indicate that oral cells obtained from patients with per-

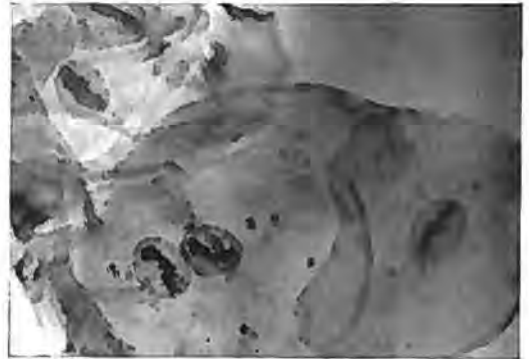


FIG. 3. Peculiar intranuclear chromatin bandings observed in a smear obtained from a clinically normal appearing buccal mucosa of a healthy female subject.

nicious and iron deficiency anemias display a tendency towards enlargement of some nuclei. Reduction in nuclear size was shown in response to treatment, and controls were also used in their studies. Their data indicate that this tendency of nuclear enlargement is erratic and occurs in a

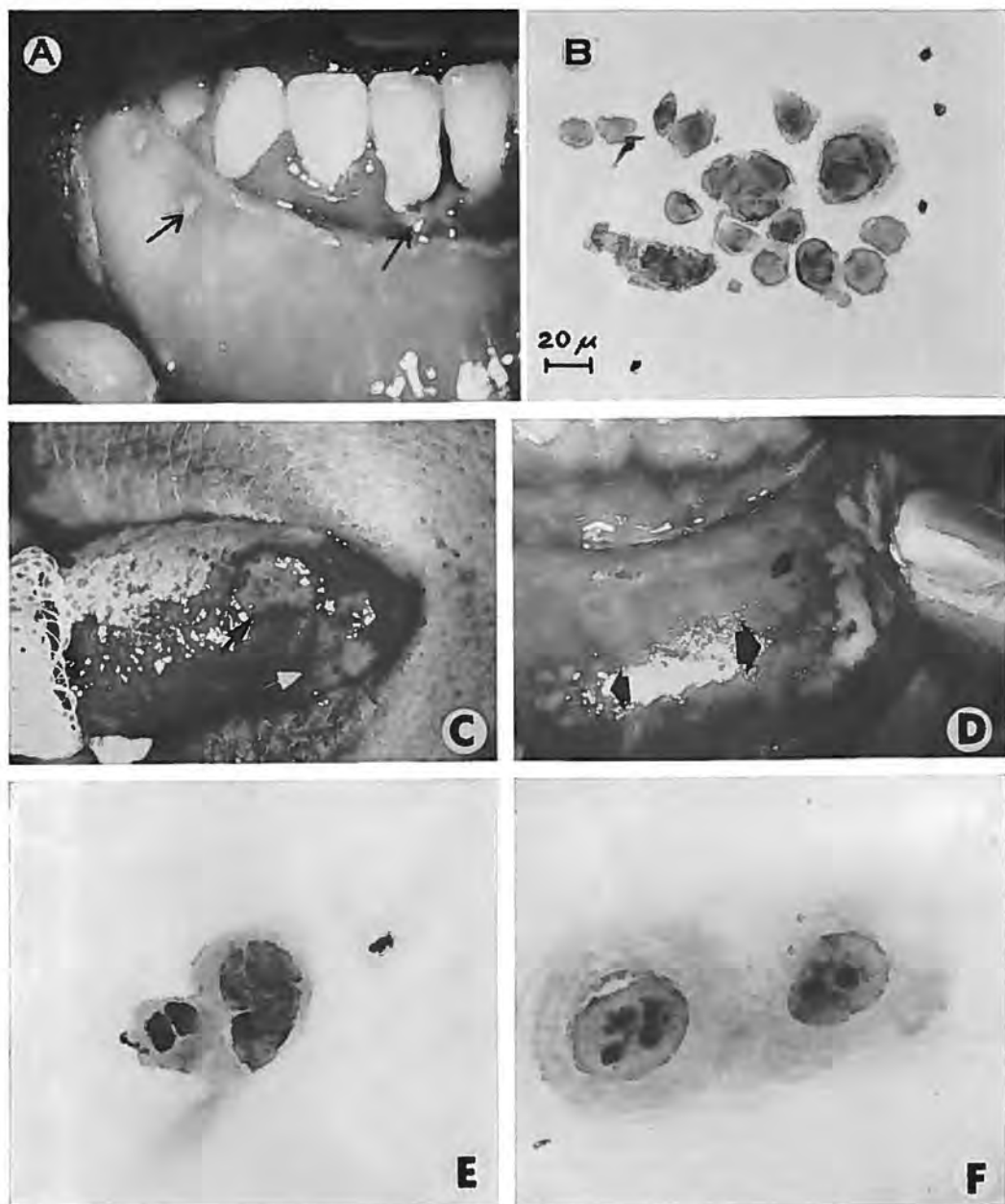


FIG. 4. A-B A 23 year old female with herpetic gingivo-stomatitis of 3 days' duration. Note aphthous-like ulcers on labial mucosa. Smear (Fig. B) was taken from the gingival ulcer and demonstrates the giant cells characteristic of this disease. The patient had a temperature of 101°F, tender cervical lymph nodes, malaise, lymphocytosis (44%), negative heterophile antibodies, and a positive rise in herpes simplex antibody titre at a 14 day interval. She was well at the end of 2 weeks with only supportive palliative care being administered.

FIG. 4. C-F An 18 year old male patient afflicted with primary herpetic stomatitis manifested by multiple painful oral ulcerations, fever, malaise and cervical lymphadenopathy of 4 days' duration. (C) Ulcers on tongue. (D) Multiple erosions and pseudomembranes of labial mucosa. (E) Giant cell demonstrating large, pleomorphic, amorphous chromatin masses obtained from tongue ulcer. (F) Enlarged nuclei with abnormal chromatin inclusion bodies or nucleoli formations seen in scraping from lip lesion.

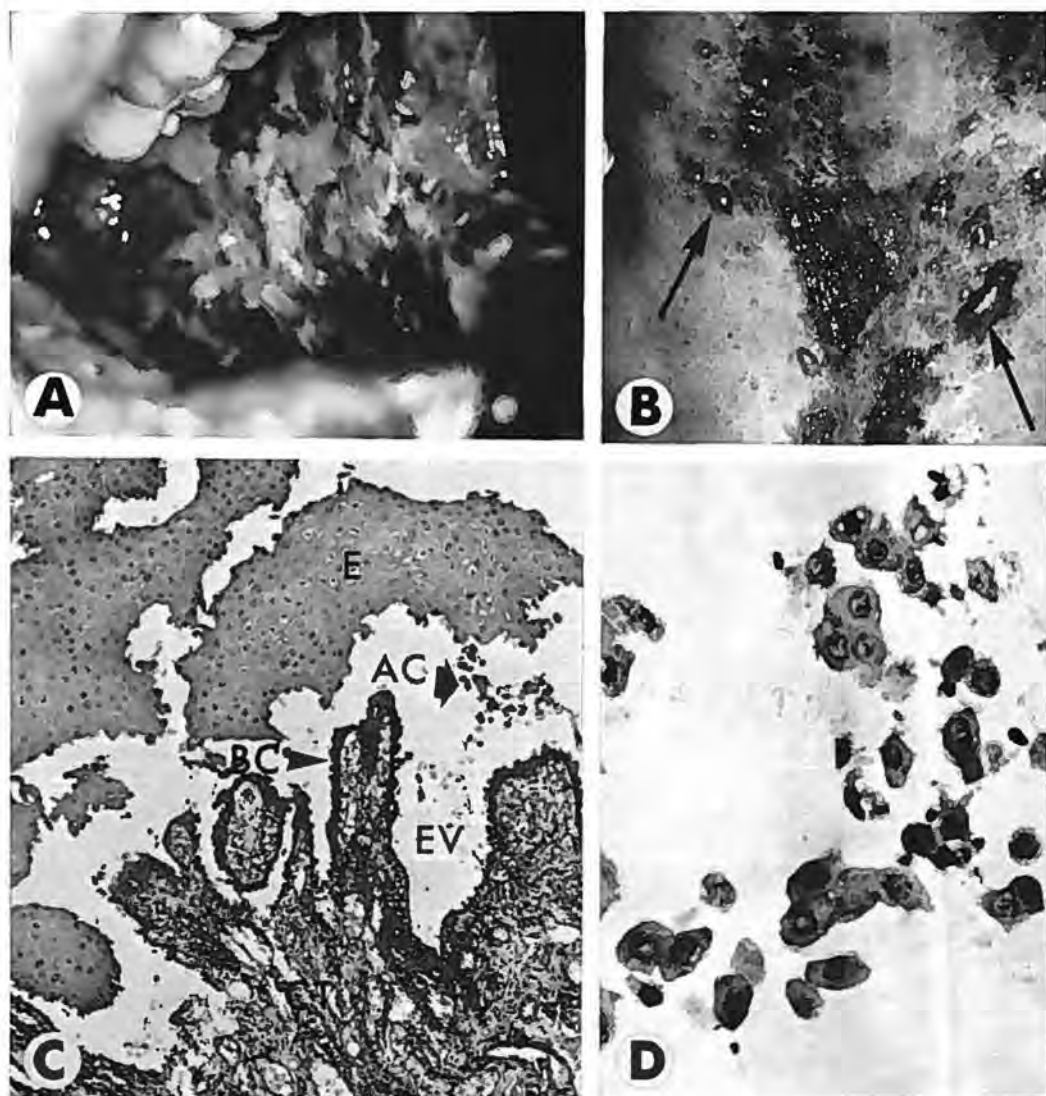


FIG. 5. A 38 year old female with pemphigus. (A) Intraoral lesions manifested by keratoses and an erythematous mucosa interspersed with multiple ulcerations. (B) Skin lesions characterized by large bullae (arrows) and areas of crusting. (C) Biopsy specimen from buccal mucosa demonstrating: E, epithelium; BC, basal cells of epithelium; EV, intraepithelial vesicle; AC, acantholytic cells; and CT, connective tissue. (D) Acantholytic cells from pemphigus vesicle.

relatively small number of measured cells. Although statistical significance of average nuclear size increase is reported and the biologic affect is of interest, the diagnostic value, practicality, reproducibility, and clinical significance are questionable. It is not uncommon in our screening procedures to detect enlarged nuclei in normal patients, and it is common in patients who are

receiving certain drugs, irradiation or chemotherapy for cancer,^{28, 10, 21} or in patients who demonstrate a variety of mucosal irritations (Fig. 2).

A peculiar nuclear chromatin banding has been reported⁵ in oral scrapings from patients with sickle cell anemia. However, we have found similar morphologic changes in some patients

without this disease (Fig. 3). These observations, therefore, do not fulfill requirements for sensitivity or specificity.

Viral Lesions

Primary herpetic stomatitis not too infrequently occurs in patients and may be confused with bacterial infections, infectious mononucleosis, erythema multiforme, blood dyscrasias or other non-specific stomatides. Tissue culture studies²⁵ have shown that the herpes virus has a capacity to induce nuclear divisions without concomitant cytologic divisions, thus producing giant cells with bizarre chromatin aberrations. Cytologic material obtained from patients with proved herpetic stomatitis (clinical findings, duration of signs and symptoms, lymphocytosis and positive interval

changes in herpes antibody titre) demonstrates these bizarre and specific cell alterations in almost all cases^{18, 3} (Fig. 4). Care must be taken to carefully observe all the morphologic changes and correlate these with clinical findings to avoid false positives for malignancy. These cytologic configurations characteristic of a viral etiology are important in managing and predicting the clinical course of this disease, since these patients may be quite ill for 10 to 15 days and establishment of a diagnosis is often difficult. Several other recent reports^{6, 12, 13} have confirmed these cytologic findings both from oral and vaginal scrapings.

Pemphigus

This disease of unknown etiology, some varieties of which used to be fatal before corticosteroids, may manifest oral lesions before the appearance of characteristic skin lesions (Fig. 5). The histopathology often reveals intraepithelial vesicles containing acantholytic cells (Tzanck cells) demonstrating nuclear pleomorphism and abnormal chromatin patterns (Fig. 5-D). Since the mouth is always extremely tender and the lesions are non-specific in appearance, biopsy usually is deferred or not performed. These acantholytic cells may be obtained from vesicular scrapings.^{3, 6} Similar appearing cells are sometimes obtained from aphthous and periadenitis aphthous-like lesions. The cells may be mistakenly interpreted as suspicious when not correlated with clinical descriptions.

Ulcerations And Inflammations

Oral mucosal responses to physical, chemical or biologic agents vary widely in clinical appearance. Scrapings from these lesions may reveal cells whose cytoplasm is abnormally acidophilic and parabasal-like cells with enlarged nuclei and scanty surrounding cytoplasm (see Fig. 2). These findings also have been described in another study.¹⁸ Infrequently, cells displaying prominent and multiple nucleoli, abnormal chromatin patterns and multinucleation will be found. These may account for suspicious appearing cells and stress the importance of correlation of clinical and microscopic findings to determine a rational course of patient management. False positives are very infrequent. Preliminary studies^{2, 20} have revealed no effects from dentures or cigarette smoking in altering the morphologic patterns of exfoliated cells.

Nasal And Antral Oral Fistulae

Openings between the oral cavity and the maxillary antrum or nasal cavity following ir-



FIG. 6. (A) Patient with oro-naso-antral fistula following surgery and irradiation for a carcinoma. (B) Suspicious columnar cells from a benign mucosal change one year after therapy.

radiation or surgery expose mucosal surfaces that usually exhibit erythematous and granulomatous-like changes which are difficult to interpret clinically (Fig. 6-A). Cytologic smears serve as a useful adjunct in evaluating these changes. The columnar cells obtained often exhibit slightly enlarged, pleomorphic nuclei, containing promi-

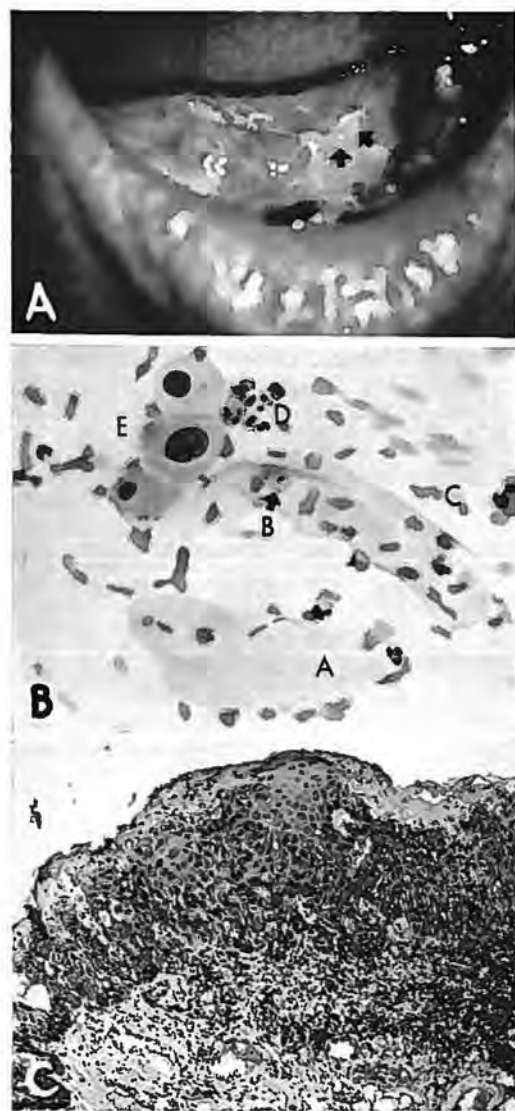


FIG. 7. (A) White patch and erythema (arrows) thought to be a benign response to heavy smoking. (B) Exfoliative cytology: A) denucleated squamous cell; B) normal squamous nucleus; C) red blood cells; D) polymorphonuclear leucocytes; and E) malignant cells. (C) Tissue section: Squamous carcinoma.

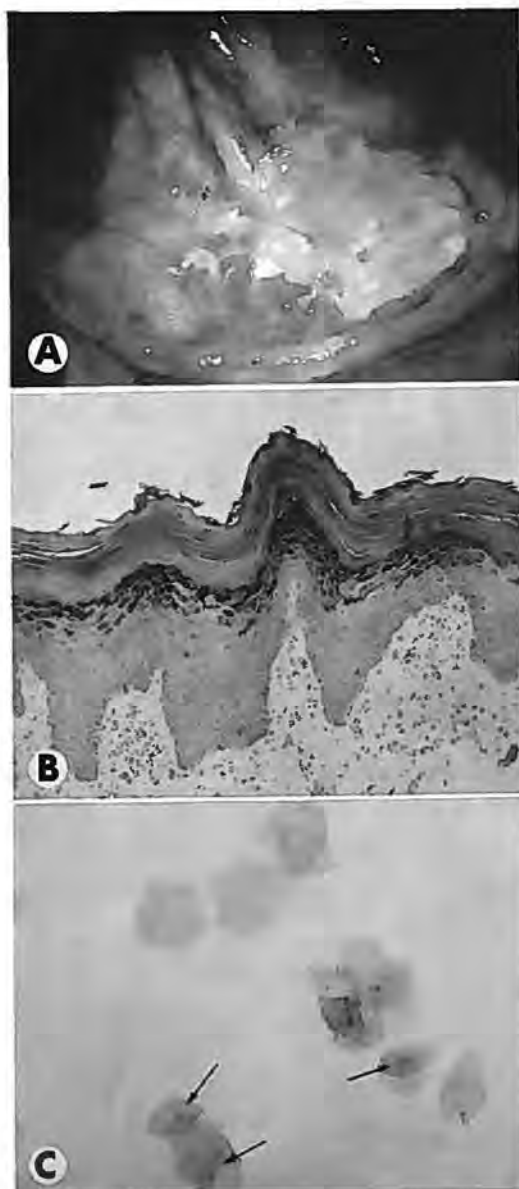


FIG. 8. (A) Leukoplakia, floor of the mouth. (B) Representative specimen demonstrating hyperorthokeratosis without any epithelial dysplasia. (C) Surface scraping prior to excision showing the surface cells to be intact and some to even contain nuclei (arrows).

nent nucleoli, and surrounded by a scanty amount of cytoplasm; and hyperchromatism may be present (Fig. 6-B). They are often interpreted as suspicious. Long term observations and occasional biopsies have indicated these morphologic changes may lead to false positive findings.

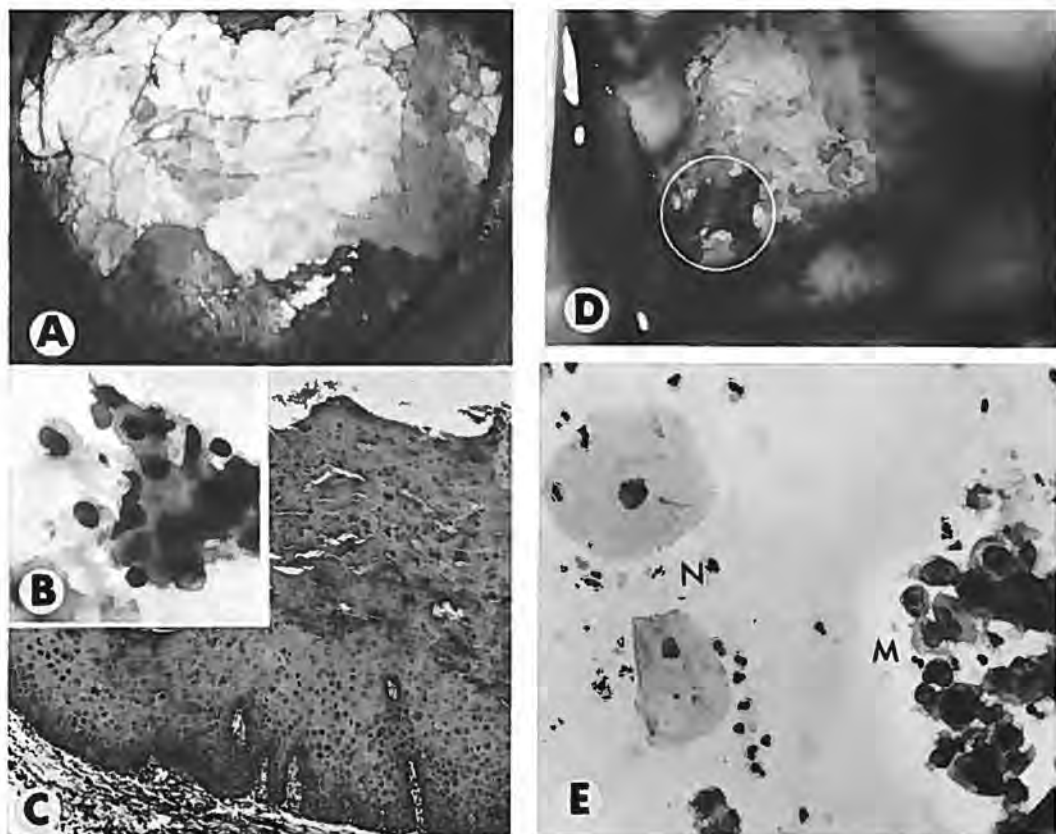


FIG. 9. (A) Leukoplakia of the tongue, 30 year duration without change and of unknown etiology. (B) Cytologic scraping revealed suspicious cells. (C) Incisional biopsy showed a hyperparakeratosis with a dyskeratosis of the stratum corneum accounting for the abnormal nuclear pleomorphism and hyperchromatism. (D) Leukoplakia of the palate interrupted with an atrophic area (circle). (E) Smear from above atrophic area revealing malignant cells (M) compared to normal cells (N).

Leukoplakia

Leukoplakia may be defined as any white plaque or patch that cannot be scraped off from the oral mucosa and cannot clinically or microscopically be diagnosed as any other condition. It occurs in less than 5% of the adult population. Studies have shown leukoplakia to be a precancerous lesion in some patients.^{15, 22} Since a dysplasia or early cancer may appear as a benign leukoplakia (Fig. 7), clinical examination should be supplemented with microscopic material. The most constant histopathologic finding is hyperkeratosis. Cytologic smears from the surface, even prior to ulceration, will yield representative cells.²⁰ This is based on the following known facts: 1) because of a relatively fast renewal time (probably less than 2 weeks), hyperparakeratotic surface cells contain nuclei representative of abnormal epithelial maturation patterns; 2) leukoplakias

that appear histologically as hyperorthokeratotic (surface appears as an amorphous mass of keratin without evidence of nuclei) in effect contain many tightly packed but intact cells, some of which contain nuclei (Fig. 8); 3) I have not observed or found in a report that a carcinoma ever has occurred solely under hyperorthokeratotic stratum corneum—a transition to hyperparakeratosis will take place first or simultaneously; and 4) carcinomas in leukoplakias most often develop in areas of atrophy and not in the areas of greatest hyperplasia and cornification (Fig. 9). Cytologic squamous atypia from these lesions demands biopsy. Persistence of leukoplakia when removal is not feasible, requires constant clinical and microscopic followup analyses. Cytologic studies^{22, 23} on the effects of high dosages of vitamin A on oral leukoplakias indicate variable degrees of decreased cornification as evidenced by increases in both nucleation and basophilia of surface cells.

In a study of some oral lesions which may resemble leukoplakia, namely white sponge nevus of Cannon, Darier-White's disease and hereditary benign intraepithelial dyskeratosis, Witkop²³ cited cytologic changes characteristic of these lesions: cell-within-cell bodies of Darier-White's disease and hereditary benign intraepithelial dyskeratosis; and eosinophilic condensations in the cytoplasm of cells from the white sponge nevus. However, these changes are non-specific and may also be found in irradiated cells, cells from patients on chemotherapy and occasionally in cells from some subjects with other benign oral conditions (see Fig. 2).

SUMMARY

Benign oral lesions occur frequently and may be confused clinically with malignant lesions. The majority of benign lesions in the oral cavity reveal degrees of acidophilia, enlarged nuclei, hyperchromatism, pyknosis, altered nuclear-cytoplasmic ratio which are so slight that they most often are not mistaken as suspicious or consistent with malignancy. These changes show no constancy or characteristics to allow this technique to be a useful tool in classifying benign oral lesions. Exfoliative cytology has been helpful in identifying patients with herpetic stomatitis and as an adjunct in supplementing clinical evaluation and histopathology in managing patients with oral leukoplakia.

Oral cytology finds its most important use in aiding the differentiation of benign changes from early malignancy. In our hands this has accelerated biopsy in unsuspected oral carcinomas and directed judgement in referral examination by a therapist as well as to the type of biopsy. Because each region of the body has its specific pathologic uniqueness, an understanding of oral diseases along with microscopic and clinical correlations is necessary for both the clinician and patient to benefit optimally from oral exfoliative cytology.

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