Section of Odontology

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President's Address

Leukoplakia Buccalis: An Enigma

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A Hungarian dermatologist, Schwimmer (1886), described leukoplakia under its present name and definitely distinguished it from psoriasis. Cade (1948) defined leukoplakia as:

'a chronic process affecting the mucous membranes of the mouth and tongue, characterised by the development of irregular pearly white patches of keratinized epithelium ultimately tending to undergo malignant change'.

This definition covers a number of different clinical entities grouped together under the title 'leukoplakia'; the term therefore provides only a tentative clinical diagnosis which must be supplemented by a histopathological description. This is a reflection of the viewpoint of a leading authority in the treatment of cancer, whose professional life covered the period of the pre-penicillin era, and a higher proportion of his patients attending his cancer clinic suffered from syphilis compared with today. In contrast, Pindborg's definition (1968) is that of the physician considering the differential diagnosis of keratinizing lesions in the oral cavity. Pindborg's (1968) definition of leukoplakia as 'a white patch or plaque, not less than 5 mm in diameter, which cannot be removed by rubbing and which cannot be classified as any other diagnosable disease', still poses the question, what then is leukoplakia, which incorporates such variable etiological factors from simple friction to syphilis? In the statistical surveys carried out by Kramer *et al.* (1970), the authors have distinguished between the simple keratosis, meaning the mild reactions to smoking and friction, from those cases in which the tissue changes were more severe, under the title leukoplakia. The latter presumably would sometimes include patients who were heavy smokers. The authors realized the two categories formed a continuous spectrum. The problem at the moment would appear to be almost insoluble and those who set up these studies or try to analyse them, sometimes find themselves going around in full circle and reaching a compromise.

Because leukoplakia is such an ill-defined word, with emotive connotations, many say the term should be abandoned. However, it is so ingrained in the literature that it would be impossible to relate it to the past. The term leukoplakia should be restricted to lesions whose histopathology shows evidence of cellular dysplasia. These lesions featuring cellular dysplasia must be regarded as premalignant lesions, as conclusively shown by many long-term studies. Furthermore, there remains the necessity to find a suitable way of communicating to the patient the degree of disquiet the tissues show.

The Recent Literature

The studies by Bánóczy & Sugár (1972) are of particular interest for they followed up 520 patients over twenty-five years during which time 31 cases became a carcinoma, i.e. 5.9%. No carcinoma occurred in the condition they called leukoplakia simplex, that is just keratinization, in 250 patients. They used the term erosive leukoplakia for Pindborg's 'speckled leukoplakia' and 28% of all the erosive leukoplakias went on to a carcinoma. They concluded that carcinomata developed mostly in leukoplakia when several factors were acting, such as smoking, alcohol, trauma, &c.

Cawson (1969) observed that the causes of leukoplakia are not necessarily those causing cancer and that there was no evidence that the removal of the lesion would prevent malignant change.

It is, however, in the computer-aided analyses (Kramer 1974) that our ways of thinking and

planning in the future will be altered. In these studies the observer records his findings without attempting to interpret these findings into a diagnosis. The problems of communication are heightened in particular in this subject of leukoplakia and many familiar words and phrases require precise definition. Kramer's studies have done much to put the quality of measurement into the measure of what we are speaking about when we use the term 'leukoplakia'.

Lehner (1970) has suggested that in leukoplakia, the carcinomatous transformation may be associated with some immunological changes, and in particular a depression of lymphocyte transformation in patients with carcinoma-in-situ, and some with epithelial atypia as compared with those showing only hyperkeratosis. This confirms what is already known about those leukoplakias featuring atypia as being more likely to develop into a carcinoma.

Pindborg *et al.* (1972) have evaluated the importance of different etiological factors in leukoplakia throughout the world and these account for the differing incidence of neoplastic change in leukoplakia in different countries. They conclude that the etiological factors analysed could not fully explain the presence or absence of leukoplakia and that other factors, so far not recognized, may also play a role. The development of carcinoma in oral leukoplakia cannot be determined only by those factors at present recognized as being involved in the etiology of oral leukoplakia.

Silverman & Rozen (1968) reported a study of 117 patients with irreversible oral leukoplakia over eleven years and one of their findings which confirms that of Cawson, is that a reversible white patch can recur and may be premalignant. By irreversible, they mean that once the cause, be it trauma or smoking, has been removed, the lesion remains. Ten per cent of the cases diagnosed clinically with leukoplakia proved on biopsy to be a carcinoma, and carcinoma subsequently developed in leukoplakia in 6% of the patients. However, in all these studies the percentage of malignancies occurring in leukoplakias cannot be directly compared, as the criteria for the diagnosis of leukoplakia and the sampling of the material vary from one investigation to another.

Thus, from the studies of a large series of cases by many investigators, there are certainly characteristic traits in leukoplakia which may appear to be of prognostic significance and may influence the therapy to be applied. The management of patients with leukoplakia is time consuming for the dental surgeon and the patient and the economic aspects of this does to some extent limit the follow up which is so necessary, sometimes through the lifetime of these patients.

Leukoplakia and Melanin

There is a paradox in the increased formation of melanin and the white patch. Butlin (1885) preferred the term 'leucoma' to 'leukoplakia' and described the patches as bluish-white, but in the third edition of Butlin's 'Diseases of the Tongue' (1931) edited by Spencer and Cade, the bluish tinge to the white patches was dropped in the descriptions of the disease. It was reported (Cooke 1956) that melanin was present in the basal layer and lower prickle cells of the epithelium and the corium of a smoker's keratosis affecting the buccal mucosa. Thus, the present author has observed cigarette smoking has the effect of keratinizing an otherwise nonkeratinized mucosa and increasing melanin formation.

Referring to this interesting and perplexing finding as it applies to leukoplakic patches on the floor of the mouth of Caucasians, who are heavy smokers (Fig 1A), in some cases the white patches have been clearly discoloured bluish-white on a dusky bluish mucosa; in other cases the lesion has appeared pearly white and histologically there has been a marked increase in melanin which was masked by the thick keratin layer. Furthermore, this increase in melanin formation, as demonstrated by Masson's silver stain, has nearly always been associated with orthokeratosis, and less so with parakeratosis. The formation of melanin is not necessarily related to the severity of the lesion, i.e. with atypia; it seems rather that pari passu with the increased formation of keratin so the melanocyte-keratinocyte unit is activated. The melanin is found in the basal cells and in the melanocytes with deposits generally within histiocytes in the corium (Fig 1B).

It is perhaps no surprise that melanin is not found within the epithelium within lichen planus, although there are occasionally very small deposits within histiocytes in the corium. There is no doubt that in past years there were many more heavy smokers in the population and that this accounted for the description of the bluish-white patches given by Butlin to the leukoplakic lesions. Furthermore, the most deeply pigmented white patches have been in those tertiary syphilitic leukoplakias. This may reflect not only the habit of smoking but also the long-standing nature of the chronicity of the mucosal changes. Cooke (1964) referred to a diffuse blue-black pigmentation giving the atrophic mucosa a dusky hue as a background to a case which after ten years developed into an oral carcinoma. At the time it was thought that this melanosis was similar to that of the long-standing inflammatory conditions affecting the skin. Paymaster (1956), in describing precancerous oral changes in India, emphasizes the significance of increased pigmentation together with submucous fibrosis.

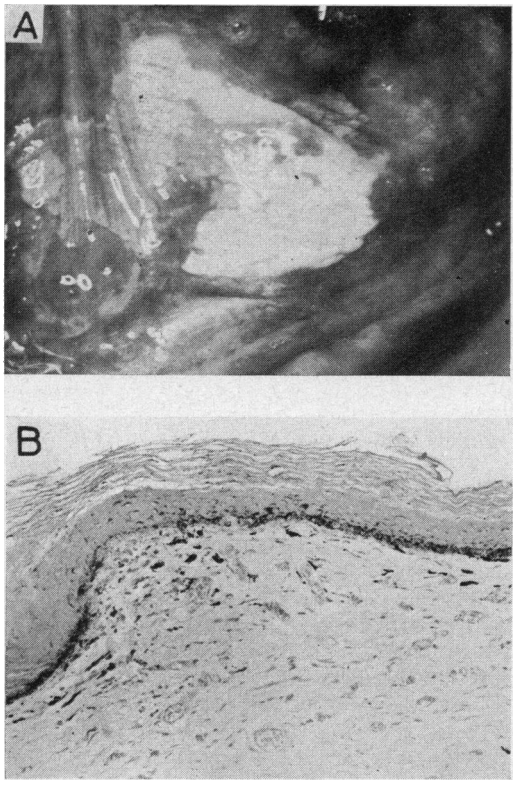

Fig 1 A, *smokers' keratosis of floor of mouth in woman aged 60 who smokes 20 cigarettes a day.* B, *section of lesion. Masson Fontana.* × *20*

Since this increased formation of melanin is associated with cigarette smoking, some of the pigmentation seen in patients' mouths may be the result of cigarette smoking, a pigmentation which might be masked clinically had leukoplakia developed at those sites. Smoking may augment an occult racial pigmentation.

Thus, increased pigmentation of the oral mucosa due to melanin, besides reflecting the chronicity of the mucosal changes, may well be the direct result of cigarette smoking. The finding of the association between increased melanin formation and keratinization may help to distinguish between smoker's keratosis, the 'ebbing tide' type of keratosis and also lichen planus.

Hypertrophic lichen planus: This, perhaps, is the most difficult condition to distinguish clinically from leukoplakia (Fig 2A). The sites of election are the dorsum of the tongue and the hard palate. The lesions are of even thickness, pure white and the margins may have a spidery pattern. It is the least common pattern of lichen planus affecting the oral mucosa and its importance lies in its persistence and the fact that the patient's life insurance may be loaded on the diagnosis of leukoplakia. However, histological diagnosis is generally unequivocal in favour of lichen planus.

There is a thick keratin layer of even thickness supported by a prickle cell layer devoid of any atypia (Fig 2B). Liquefaction degeneration of the basal cells is patchy and there is a fairly intense lymphocytic infiltration associated with the bases of the epithelial ridges.

Because lichen planus is rarely reported as affecting the hard palate, some patients who are said to have leukoplakia may well in fact have had hypertrophic lichen planus.

Erosive lichen planus: Erosive lichen planus is an unpleasant and troublesome condition, therapeutically somewhat intractable, and the atrophic mucosa may ulcerate at the slightest trauma throughout the patient's life. In some of these patients, erosive lichen planus affects the tongue in quite a characteristic pattern over the years (Fig 3A). From the features of erosive lichen planus, the clinical appearance becomes indistinguishable from leukoplakia (Fig 3B). The patches of keratinization develop at the site of former long-standing chronic erosions and the change may be localized to one area or affect the whole dorsum of the tongue.

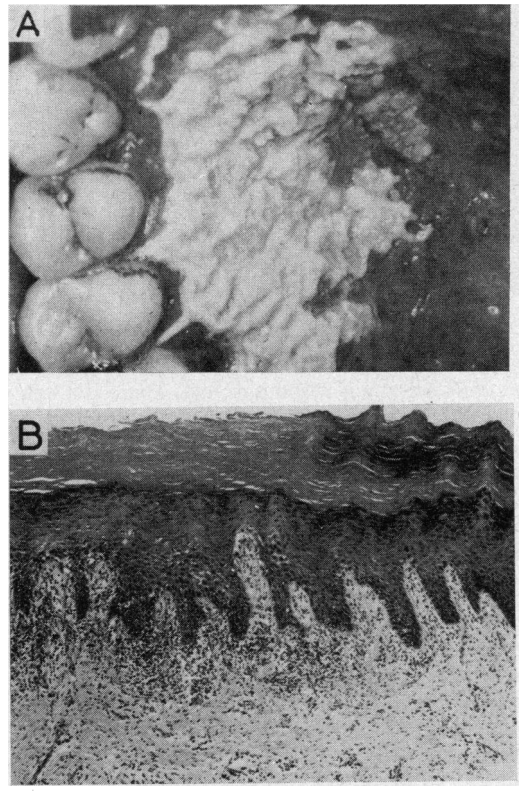

Fig 2 A, *hypertrophic lichen planus of hard palate.* B, *section of lesion. H & E.* × *10*

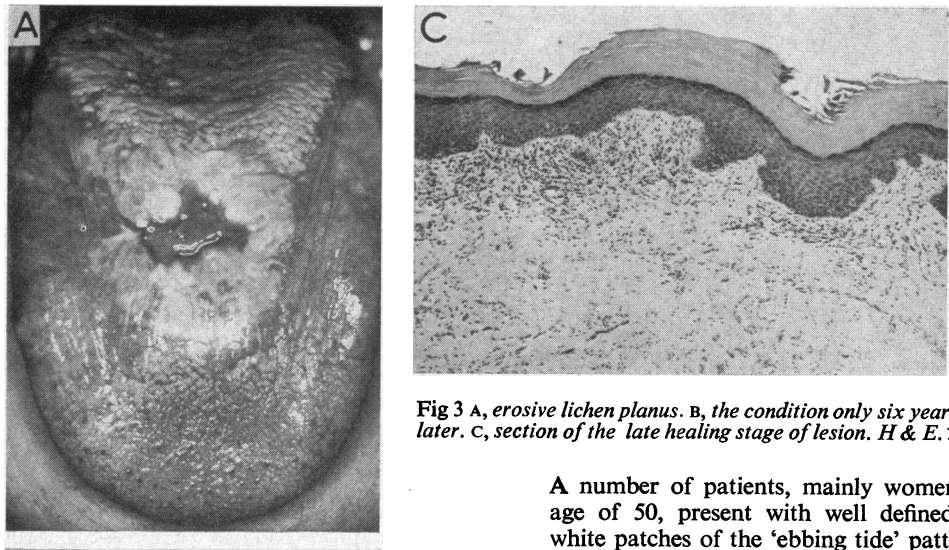

Fig 3 A, *erosive lichen planus.* B, *the condition only six years later.* C, *section of the late healing stage of lesion. H & E.* × *10*

There is thus a transition in time of the histological appearances from erosive lichen planus to a simple keratosis without atypia. There is a light subepithelial lymphocytic infiltration and liquefaction degeneration of the basal cell layer becomes minimal (Fig 3C). It is very difficult in these cases to decide whether this is a simple keratosis, alternatively called leukoplakia simplex or whether in the light of the clinical history this has a definitive histological diagnosis as the healing stage of atrophic lichen planus. It is in such a case that cluster analysis, carried out in a computer aided study by Kramer *et al.* (1970) will be of value in establishing histological diagnosis.

'Ebbing tide' pattern of leukoplakia simplex: There is considerable controversy whether this pattern of keratinization differs in any way from smokers' keratosis. The author believes it does, particularly when it is found in non-smokers. A number of patients, mainly women over the age of 50, present with well defined wrinkled white patches of the 'ebbing tide' pattern on the gingiva. These lesions are sometimes wrinkled, white, well defined, but loss of suppleness is difficult to define in that area (Fig 4A). They are symptomless and mainly in non-smokers, but even if the patient smokes there may be no other mucosal changes. On histological examination the junction between the hyperkeratosis and the keratosis is clear cut, there is no atypia, or melanin formation and the lesions do not recur after operation (Fig 4B).

The author agrees with all the comments on the lack of evidence that these lesions are developmental, but in the light of the changes shown in the oral mucosa following long-standing ulceration and inflammation from erosive lichen planus, the possibility arises that these gingival lesions might result from the involution of a former lichen planus presenting as a desquamative gingivitis. Whatever their etiology, they appear to be a well-defined entity, localized and without any field change. However, there is always the liability that subjected to further irritation, such as smoking and friction, this altered epithelium may feature atypia and so go on to a carcinoma, as was the case in the example given by Pindborg *et al.* (1972) of an 'ebbing tide' lesion affecting the floor of the mouth.

Atrophy of the oral mucosa and keratinization: There are now well documented case histories of patients affected by atrophic lichen planus, chronic discoid lupus erythematosus, candidiasis, as well as leukoplakia progressing to a carcinoma. In all the large series of leukoplakia becoming a cancer it is speckled leukoplakia (better called by Kramer (1974) speckled erythroplasia), that is generally referred to, a condition which the author has previously termed senile keratosis, with the flecks of keratin on an atrophic erythematous mucosa. The common denominator for all these

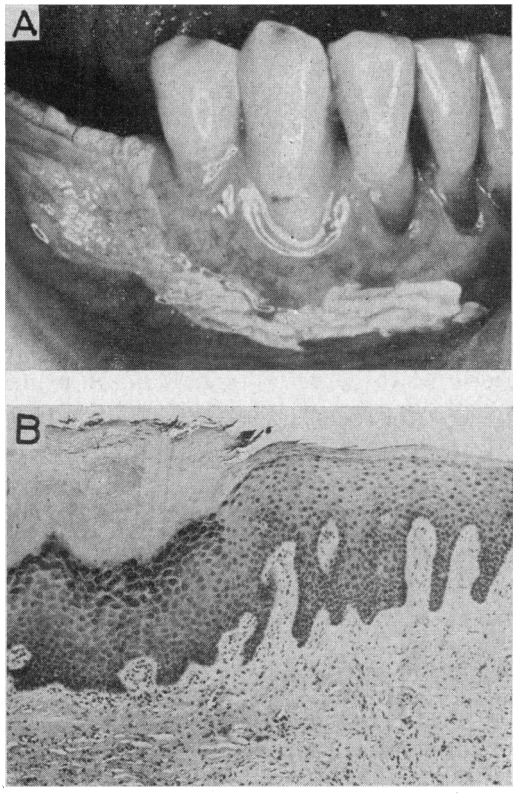

Fig 4 A, *the ebbing tide pattern of leukoplakia simplex.* B, *section of lesion. H & E.* × *12*

conditions is atrophy of the oral mucosa and this I believe to be the most important premalignant condition in the mouth and not necessarily the disease which is superimposed upon it. This atrophy, sometimes associated with diminished flow of saliva, again is the basic common denominator to the predisposition of malignancy in the upper alimentary tract in women with long-standing iron deficiency anæmias. Whereas rarely are carcinomata arising from white patches seen in the mouth, apart from the lips, there are few carcinomata which are not associated with an atrophic mucosa. This atrophic mucosa is identified by its satiny, smooth dry appearance with loss of normal landmarks and subject to excoriations and ulcerations from the slightest trauma or infection. The etiology of this atrophy is, therefore, really more important than the etiology of the superimposed white patch, be it resulting from trauma, smoking, or other causative agents.

Conclusions

The common denominator for the various conditions which are regarded as precancerous in the oral cavity is atrophy of the oral mucosa. In the future, the emphasis will move away from the white patch to the study of the mucosa adjacent to it. The white patch is such a striking clinical phenomenon that just as it has masked the melanin, so it has preoccupied our energies out of all proportion to the studies that should perhaps be made of the accompanying atrophic mucosa.

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Paper

The Differentiating Tooth and Developmental Pathology

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Congenital malformations are an important cause of morbidity and mortality in man. Among individuals aged from 0 to 15 years, malformations account for more hospital days of bed occupancy than any other single group of conditions, utilizing 190 beds per day per million in 1968 (*see* Leck 1974). This morbidity is common to many communities and world-wide studies give rates of major malformation between 23 and 27 per thousand total births. Neel (1974) suggests that comparable or perhaps higher figures are found for primitive and isolated tribes, suggesting that