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Oral Precancer: Preventive and Medical Approaches to Management

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Leukoplakias are among the most common potentially malignant oral lesions. Some are idiopathic, others are related to habits such as tobacco and/or alcohol use. Medical management includes reducing or abandoning these habits, increasing the intake of fruit and vegetables in the diet, and possibly the use of active agents. Retinoids, carotenoids and topical cytotoxic agents show promise, and newer therapies are on the horizon.

Keywords: oral cancer, leukoplakia, diet, vitamins, cytotoxic agents, prevention

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POTENTIALLY MALIGNANT ORAL LESIONS

EPITHELIAL DYSPLASIA is generally regarded as heralding malignant change [1], can be seen in some leukoplakias and most erythroplasias but can, in fact, be seen in a range of oral mucosal lesions [2, 3]. Epithelial dysplasia can, in some 7–13% of cases of leukoplakia, progress to carcinoma [2, 4–15] but some lesions regress spontaneously [2, 5, 7, 14, 16].

Leukoplakia is a clinical description indicating a white plaque that cannot be clinically or pathologically characterised as any other cause of a white oral lesion (such as lichen planus, lupus erythematosus, or candidosis) [17]. Leukoplakia is in fact a heterogeneous group of lesions of different aetiologies and potential for malignant change [18].

Most leukoplakias—up to 80% in large series—are benign with no evidence of dysplasia [19], and no predisposition to malignancy, but clearly biopsy is indicated to define the remaining 10–20% that are either dysplastic or already invasive carcinomas [20]. Unfortunately, there is currently no histological or other means of reliably predicting which leukoplakias are indeed potentially malignant [21]. Overall the rate of malignant transformation of leukoplakias is of some 3–6% over 10 years but rates much higher have been reported [12, 13, 22, 23]. The potential for malignancy appears higher in certain at risk sites (floor of mouth/ventrum of tongue: lower lip; commissures); where the lesion is associated with Candida species; or where the lesion is verrucous or mixed with red lesions (erythroleukoplakia or speckled leukoplakia) [8, 12].

Leukoplakia is more common with increasing age and tobacco use [24–28]. Tobacco-associated leukoplakias vary from the benign smoker's keratosis affecting the palate to those associated with tobacco chewing or snuff use, some of which may have potential for malignant change [29, 30]. Candidal leukoplakias are more likely in tobacco smokers and have a high premalignant potential [31–35]. Nevertheless idiopathic leukoplakias have about an 8-fold higher rate of malignant transformation than those with an obvious cause [10]. Where leukoplakia is associated with oral cancer, there is also a high incidence of multicentric carcinomas [36, 37]. This paper however, deals mainly with leukoplakias.

Less common, but more sinister than leukoplakias, are erythroplakias, since virtually all are dysplastic or carcinomatous [38–40].

HABITS PREDISPOSING TO ORAL POTENTIALLY MALIGNANT LESIONS

Many patients with oral potentially malignant lesions have no identifiable predisposing factors but, in some, habits may be responsible.

Tobacco and alcohol use

Many patients with oral leukoplakia use tobacco and alcohol [41]. Tobacco is smoked as cigarettes, cigars or in a pipe and, in some instances may be chewed. Tobacco use can predispose to leukoplakia [42–44] and cancer appears to develop more frequently in those using tobacco, or alcohol [45].

Tobacco is used either alone or in special forms which may contain additives such as slaked lime or betel (see below). N-nitrosamines are the compounds thought to be the major carcinogenic agents in tobacco.

By 1988, both tobacco smoking [46] and alcohol consumption [47] had been accepted as independent risk factors for oral cancer (oral squamous cell carcinoma). Smokeless tobacco and betel quid chewing are also risk factors [48]. Alcohol topically also enhances experimental carcinogenesis [49] and the use of alcohol-containing mouthwashes may be a risk factor for oral cancer in a very small sub-group of non-smoking, non-drinking women [50].

There is convincing evidence that the combined effect of tobacco and alcohol on predisposing to intraoral cancer is greater than would be expected from the risks of each individually since there have been results showing the

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combined effect to be greater than the additive effect of the two risk factors [51] although this has not always been found [52]. The effect of smoking falls off soon after smoking ceases [53–55].

Some fairly recent studies have helped elucidate these areas. Blot *et al.* [53] in a case-control study in U.S.A. found the risk for oral (and pharyngeal) cancer to increase with increasing cigarette consumption and independently with increasing alcohol consumption. The risk among non-drinkers increased with the amount of tobacco smoked and risks among non-smokers increased with the level of alcohol intake. Among those who both smoked and drank, the risk tended to combine in a multiplicative fashion. Those who consumed daily two or more packs of cigarettes and had more than four alcoholic drinks had a 35-fold increase in risk compared to non-smokers/non-drinkers. After stopping smoking for 10 or more years, there was however, no excess risk. Another case-control study in the U.S.A. recently supported a role for cigarette smoking and alcohol consumption [56].

A case-control study in Italy showed that the risk increased strongly with increasing tobacco consumption [54] but following smoking cessation in males, the risk reduced to that of non-smokers by 5 years. Another study from Italy [57] showed considerable risk increases with alcohol and tobacco use, with risk decreasing with increasing years since cessation of tobacco use. The risk of oral and pharyngeal cancer was increased 80-fold in the highest levels of smoking and alcohol consumption considered compared to abstainers. Similar findings were reported subsequently [57].

Cigarettes can be classified as low or medium if the tar yield is below 22 mg, and as high if tar yield is above 22 mg. Compared with non-smokers the risk of oral cancer for smokers using low to medium tar cigarettes is 8.5 and for high tar cigarettes is 16.4 [58].

A case-control study from Brazil also found increased risks among cigarette or pipe smokers with a strong dose–response relationship between the number of pack-years smoked and oral cancer risk [55]. Risk among ex-smokers dropped to a level compatible with that of non-smokers 10 years after having quit smoking. A case-control study from Uruguay showed dark tobacco as having a risk more than 3 times that of light (blond) tobacco [59].

In a study of oral cancer in India, Sankaranarayanan *et al.* [60] found, among males, significantly increased risks in relation to pan-tobacco-chewing, bidi smoking and bidi-plus-cigarette smoking. Alcohol also emerged as a significant risk factor. Two recent studies from India confirmed the association between pan-tobacco-chewing and oral cancer [61, 62].

A case-control study of oral cancer in China [63] showed tobacco smoking to be a significant risk factor especially for smokers of pipes. The combined effects of tobacco smoking and alcohol consumption appeared to be approximately multiplicative [63].

Alcohol, particularly in persons who smoked tobacco was also a risk factor in other recent studies—in Uzbekistan [64], Hawaii [65] and Israel [66].

Smokeless tobacco

Smokeless tobacco contains a number of carcinogens and therefore, particularly in view of the fact that snuff can produce oral leukoplakia and carcinoma, its use is to be deprecated especially because this form of smokeless tobacco is held in the mouth for very long periods, and is popular with children and adolescents [30, 67–77]. There is clear concern about the possible carcinogenicity and other adverse effects of the snuff now sold in small "teabag" pouches [78, 79]. There is some limited evidence for an association between the use of such smokeless tobacco and oral cancer [75, 80–88].

Mouthwash use

In a U.S. study based on 125 cases of oral cancer in women and a control group of 107 [89] no association was found between mouthwash use and cancer. Patients with oral cancer did report more frequent use of a mouthwash to "disguise the smell of tobacco . . . (and) . . . alcohol" but using a mouthwash appeared in these instances to be a proxy for exposure to tobacco or alcohol. However, a recent larger U.S. study [90] found that, *after* adjustment for tobacco and alcohol use, the risk of oral cancer among users of mouthwash was increased by 40% in men and 60% in women. The increased risk was apparently only when using mouthwashes of a high alcohol content (25% or higher). Thus, it appears that the risk from alcohol in mouthwashes is similar, at least qualitatively, to that of alcohol used for drinking, although in terms of attributable risk the contribution of mouthwash use to oral cancer remains small.

Other liquids

Particular types of tea (mate) consumed in Latin America may be associated with oral cancer [55, 59].

Marijuana use

There have been some case reports of oral cancers in marijuana smokers [91, 92] but these have yet to be supported by an epidemiologic study.

Oral health

A poor dentition, as reflected by missing teeth, emerged as a risk factor independent of other established risk factors in studies from China [93]. These who did not brush their teeth regularly also had an increased risk of oral cancer over those who brushed.

Generally similar findings were reported from a case-control study in Brazil with a higher risk of oral cancer among those who reported teeth-brushing to be infrequent compared with those who brushed their teeth daily [55]. There have been similar findings from the U.S.A. [56]. The overall message appears to be that poor oral hygiene is independently associated with an increased risk of oral cancer.

Socio-economic status

Recently the relationship between socio-economic status and oral cancer risk was explored [94]. Three indicators of socio-economic status were considered (education, occupational status, and percentage of potential working life in employment). After adjustment for established risk factors, the third index only was found to have an independent association with oral cancer risk—consistent with the hypothesis that behaviours leading to social instability, or social instability itself, are linked to an increased risk of oral cancer.

Betel use and other habits

There is some confusion over the use of the term betel. Betel leaf is derived from the betel vine while nuts from the betel palm are termed areca nuts. These two products may be used orally alone, together, or together with other material such as tobacco, slaked lime, and other additives. In Papua New Guinea slaked lime (but not tobacco) is a prominent component of 'betel': in other areas tobacco may be a main component [95].

The risk of oral cancer is increased in persons who chew betel whether or not tobacco is present [96]. Areca nut use clearly predisposes to oral submucous fibrosis, a recognised premalignant condition [97–99], can cause cytogenetic changes whether tobacco is or is not used [100–102] and can result in the appearance of N-nitroso compounds in the saliva [103–108]. Areca nut-specific N-nitroso compounds can also cause epithelial changes *in vitro* [109] and can enhance experimental carcinogenesis [110–112].

Fruit and vegetables

Evidence has been accumulating to show that a low intake of vegetables and fruits is associated with an increased risk of oral and some other carcinomas [113–119]. The reason for the protective effect of a diet high in vegetables or fruits is unknown, but vitamins A, C and E and related compounds may be factors [118–121]. Vitamins A, C and E may all have anti-oxidant activity and it may be that they could be protective by virtue of this [122]. Certainly dietary beta-carotene (vitamin A precursor) does appear to reduce rates of epithelial neoplasms [123] and studies of serum levels of vitamin A in patients with head and neck carcinoma have shown low levels of retinoic acid-binding protein and vitamin A itself [124–129]. Oral carcinoma cell lines have abnormal expression of retinoic acid receptors [130]. This is discussed further, below.

MANAGEMENT OF ORAL PRECANCER

There is remarkable lack of consensus on the most appropriate management of leukoplakia—the most commonly recognised premalignant lesion [131, 132] though obviously diagnosis is an essential stage [133]. Primary prevention must be the goal [134]. Many clinicians surgically remove leukoplakias, but the patients remain at risk after operation for relapses, for developing new leukoplakias, and for developing cancers inside and outside the oral cavity [12, 19, 41, 135]. For example, a recent study of 167 patients who had their oral leukoplakia resected by CO_2 laser showed problems in 69 patients over the subsequent 5 years [41]. Relapses were seen in 31, new leukoplakias in 27, oral carcinomas in 5, tumours elsewhere in 6 (lung, skin, colon, pancreas), and most of these problems were in older patients with large lesions.

Behaviour modification

Cancer appears more frequently in persons who do not stop alcohol or tobacco use [7]. Nevertheless, leukoplakias in non-smokers appear to have a higher risk of progression to cancer [12, 17, 135]. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped [12, 136]. Leukoplakias induced by smokeless tobacco may resolve if the habit is stopped [137]. Some candidal leukoplakias respond, at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress [138]. In view of the evidence linking alcohol and tobacco, betel, and diet, to the development of potentially malignant and malignant oral epithelial lesions, it would seem reasonable therefore, that habits such as the use of tobacco and alcohol should be actively discouraged, and a good diet and oral hygiene encouraged. Unfortunately, only a few patients change their habits [26, 41, 139, 140].

The effects of dietary or oral hygiene modification on leukoplakia appear not to have been studied.

Medical treatment of leukoplakias

There is great appeal in the possibility of medical treatment of leukoplakias particularly if an agent that was effective, safe and produced lasting benefit could be found. This is particularly important, since changes may be present in mucosa that clinically may seem normal [141] and local treatment of a lesion may therefore be inadequate.

Vitamin A and related compounds (retinoids and carotenoids) are currently being examined as potential agents [142–146], though it is over 30 years since the first attempts at such treatments [147–149].

Carotenoids and retinoids

Some carotenoids have antioxidant or anticarcinogenic activities, and can block genotoxic activity of oral carcinogens such as extracts of areca nut [150].

Retinoids are the synthetic and natural analogues of vitamin A. There are many naturally occurring retinoids, including retinol, retinal, retinoic acid and their metabolites. Beta-carotene is a natural precursor of vitamin A. For over 30 years, there have been attempts to treat leukoplakias with vitamin A or analogues. Unfortunately, though in earlier studies many leukoplakias regressed or resolved during treatment with vitamin A [147–149, 151–155], vitamin A palmitate [156], or vitamin A acids [157], the unwanted side-effects and recurrences of the leukoplakias after cessation of therapy inhibited developments in this area. More recently, however, etretinate [142, 158–160], 13-cis-retinoic acid [161–163] and other retinoids have been successfully used.

Retinoids can inhibit the development of experimental oral leukoplakia and carcinoma and can reverse the effects of carcinogens *in vivo* [164, 165]. 13-cis-retinoic acid [166, 167], retinyl acetate [168] and beta-carotene [169–171] can all have tumour-suppressive activity in animal models of oral carcinogenesis. Unfortunately, however, though topical 13-cis-retinoic acid in some studies inhibited tumours induced in hamsters by 7,12-dimethylbenz(a)anthracene (DMBA), over half the animals died from hepatic and renal toxicity [172], and a few workers have failed to find a beneficial effect from 13-cis-retinoic acid [173]. Furthermore, though retinoids can suppress tumour development in animals exposed to carcinogens, neoplasia may appear on cessation of retinoid treatment [164, 174, 175].

Exactly how retinoids may act to inhibit carcinogenesis is unclear although some retinoids may enhance anti-tumour immune responses [176, 177] and retinoids have a pronounced and essential effect on cell differentiation [178]. Retinoids may have an effect by their interaction with growth control mechanisms such as transforming growth factors [179] and thus also oncogenes such as the *jun–fos* complex [180], and possibly by acting on tumour suppressors either directly [181]

*Table 1. Main chemoprevention trials using retinoids or carotenoids in oral leukoplakia**

Author	Year	*n*	Agent	Overall response (%)
Silverman *et al.*	1963	16	Retinol	43
Raque *et al.*	1975	5	Retinoin	100
Koch	1978	24	Isotretinoin	87
		24	Etretinate	91
		27	Tretinoin	59
Cordero *et al.*	1981	3	Etretinate	100
Koch	1981	24	Etretinate	83
		21	Etretinate	71
Shah *et al.*	1983	11	Isotretinoin	100
Hong *et al.*	1986	24	Isotretinoin	67
Stich *et al.*	1988	27	Beta-carotene	15
		51	Beta-carotene/vitamin A	27
Stich *et al.*	1988	21	Vitamin A	57
Lippman	1990	56	Isotretinoin/beta-carotene	55
Garewal *et al.*	1990	24	Beta-carotene	71
Toma *et al.*	1990	15	Beta-carotene	27
Toma *et al.*	1992	16	Isotretinoin	36
Chiesa *et al.*	1992	115	Fenretinide†	95

*The results of several other trials have yet to be reported.
†Examined recurrences after surgery.

or again via an interaction with transforming growth factors [182, 183]. Retinoids may also inhibit transformation mediated by papillomaviruses [184].

Human oral leukoplakias have been treated with a range of retinoids and carotenoids (Table 1). Leukoplakias have been successfully treated with systemic 13-cis-retinoic acid [16, 185, 187], vitamin A [188–192], aromatic retinoids [142, 159, 160, 193] and beta-carotene [194–199]. Topical applications of vitamin A acid have also been effective in some studies [156].

In a study at the MD Anderson Institute, U.S.A., systemic 13-cis-retinoic acid (isotretinoin) produced some regression of oral leukoplakias but did not necessarily eradicate the lesions. The study group of persons with leukoplakia were randomly assigned to receive placebo (20 patients), or 13-cis-retinoic acid (24 patients). The lesions regressed in 67% of those on the isotretinoin at 1–2 mg/kg per day for 3 months, and in 10% in the placebo group. Dysplasia was reversed in 54% of those on isotretinoin and in 10% in the placebo group. Unfortunately, though toxic effects were said to be acceptable to most patients, the leukoplakias in over half of the responders had recurred by 3 months after treatment ended [16]. Isotretinoin at 1.5 mg/kg per day for 3 months followed by 0.5 mg/kg daily for 9 months resulted in an initial 55% beneficial response followed by maintenance of effect in 92% [200].

Isotretinoin causes severe adverse reactions at doses above 0.8 mg/kg/day but at lower doses (0.2 mg/kg/day for 3 months, doubling doses for a further 3 months, then increasing by 0.2 mg/kg for 3 months and so on) has been seen to be beneficial in oral leukoplakias [187]. An objective response rate of a 50% or more reduction in lesion size was seen in 36%: unfortunately occasional patients regress in time.

Other synthetic retinoids have also recently been tested and some have less adverse effects than isotretinoin. Fenretinide (N-4-hydroxyphenyl-retinamide: 4-HPR) 200 mg daily used for 1 year, reduced the relapses and appearance of new oral leukoplakias compared with controls, with few adverse effects, in 39 patients having previously had leukoplakias surgically excised [193]. Only 3 of 39 patients on 4-HPR had relapses or new leukoplakias compared with 12 of 41 controls, and though 54% of those on 4-HPR had some adverse effects (mainly dermatitis, skin or mucosa dryness, or abdominal discomfort), only 16% withdrew because of these effects. It is as yet unclear whether this agent can inhibit the appearance of neoplasms.

A study from the MD Anderson Institute found that 13-cis-retinoic acid produced a significant reduction in second primary tumours in cured head and neck cancer patients [201]. However, the toxicity of systemic 13-cis-retinoic acid at 50–100 mg/m^2 surface area was considerable. Such toxicity may be reluctantly acceptable in patients with an existing cancer but is unacceptable in those with only potentially malignant conditions.

In a study from Arizona, U.S.A., beta-carotene alone in a dose of 30 mg daily for 3–6 months also produced a 71% response rate in 24 patients with oral leukoplakias, with no significant toxicity [195]. The same workers have used beta-carotene 60 mg daily for 6 months and report similar benefit [197–198]. Others have found beta-carotene 90 mg daily to produce benefit in 44% after 3 cycles of use of 3 months each [199]. Similar benefits from beta-carotene in Western populations have yet to be found by others [202] and one group has found it less effective than isotretinoin [200]. However, beta-carotene with vitamins C and E may have some benefit [203, 204] and systemic vitamin A and beta-carotene were shown to be beneficial in oral leukoplakias in tobacco/betel nut chewers from Kerala, India. 21 patients given a short-term randomised trial of vitamin A 0.14 mg/kg weight for 6 months had complete clinical remission in 57% which was substantiated cytologically and histologically. A series of studies showed that vitamin A plus beta-carotene produced regression in 28% and beta-carotene alone produced regression in 15% [188–192, 204]. The clinical benefit extended for up to a further 4 months after cessation of therapy, though cellular chromatin patterns typical of leukoplakias could be seen on biopsy: clinical benefit could be maintained for at least an additional 8 months by administering continued lower doses of vitamin A or beta-carotene [190–192].

Unfortunately, the improvements in oral leukoplakia produced by treatment with most of the vitamin A related compounds used to date have often been accompanied by adverse reactions which have included especially cheilitis, facial erythema, desquamation, conjunctivitis and photophobia, hypertriglyceridaemia, and liver damage. This toxicity has been the main limiting factor in the use of retinoids and there is also the possibility of teratogenicity. Toxicity was a particular problem in early studies. Koch randomised 72 patients in three groups: isotretinoin (13-cis-retinoic acid), tretinoin (beta-all-trans retinoic-acid) and etretinate [142, 159]. Partial response was found in 59–91% in the three groups but the mucocutaneous toxicity was considerable. In other, non-randomised studies comparable responses were obtained with these retinoids [160–205].

The mechanisms of retinoid toxicity are unclear but prostaglandins may be released by some retinoids, and inhibitors of prostaglandin synthesis protect against toxic effects, at least in animals [206]. Interestingly, retinoids of low toxicity—such as 4 hydroxyphenyl retinamide—decrease prostaglandin synthesis [207]. Furthermore, retinoids are expensive. The cost of treatment with isotretinoin 1 mg/kg/day for 3 months is approximately £270 [132].

Modulation of cellular differentiation and proliferation by compounds such as some of the newer retinoids thus offers the possibility for the therapeutic prevention, reversal, or arrest of carcinogenesis. The long-term results of other trials, including those using low dose 13-cis-retinoic acid (less than 0.3 mg/kg/day) which showed a 50% or more reduction in lesion size in 36% of patients [186], or 4-hydroxyphenyl retinamide 200 mg daily [193], or those using natural vitamin A (retinyl palmitate) as in the EUROSCAN study of the EORTC [208, 209] and others (Table 1) are thus awaited with great interest.

Vitamin C

Though with vitamin C there is epidemiological evidence of reduced cancer risk [210], there is no evidence of a reliable protective effect against oral lesions, though some studies suggest an effect (see above).

Vitamin E

Vitamin E has synergistic inhibitory activity against carcinogenesis in animal models [211–214] and may have some beneficial effect in man [203, 215–219].

A recent multicentre study in the U.S.A., using vitamin E in oral leukoplakias showed a beneficial clinical response in 46% of 43 patients by 24 weeks, and a histological response, with no serious adverse effects [216]. Another study, from Uzbekistan, showed a significant decrease in oral leukoplakias after combined treatment with vitamin E, retinol and beta-carotene [217]. Vitamin E therefore, shows promise in the control of leukoplakias.

Topical chemotherapy

Topical treatments of leukoplakia with podophyllin solution [220] or bleomycin [221–223] has induced some regression or even total resolution of dysplasia and of clinical lesions. Bleomycin (15 mg) dissolved in four or five drops of dimethylsulphoxide is applied topically once a day for 10 consecutive days. During this period the epithelium is usually shed and appears clinically and histologically normal on re-biopsy 2 months later. There are cost implications for bleomycin therapy—presently a 10 day course would cost approximately £160 [132].

Iontophoretic application of bleomycin has been used to treat premalignant lesions and carcinomas [224, 225] as has local injection [226]. Topical application of oil bleomycin to carcinomas even has some favourable effect [227] but since carcinomas can recur after *systemic* bleomycin therapy [228] extreme caution should be exercised when topical agents are used, and patients must be carefully followed up.

Iontophoretic application of cisplatin has recently been used to treat cutaneous squamous carcinomas [229] but has not been used on oral lesions.

Newer treatments

Polyamine inhibitors. Polyamine metabolism is altered in oral, and other, carcinomas [230–232] and inhibitors of polyamines may have a future role in chemoprevention of carcinoma [233, 234]. Studies have shown a protective effect of polyamine biosynthesis inhibitors such as difluoromethyl ornithine, an ornithine decarboxylase inhibitor [235] and of indomethacin and piroxicam, both prostaglandin synthesis inhibitors [236], on 4 nitroquinoline 1-oxide-induced oral carcinoma in rats. Prostaglandin E_2 (PGE_2) levels are high in head and neck carcinomas [237] and might impair host immune responses. Administration of prostaglandin inhibitors such as indomethacin can inhibit animal oral carcinogenesis [238], and can induce some tumour regression in man [239] possibly related to an increased mononuclear cell infiltrate in and around the tumour [240].

Glutathione S-transferase stimulators. Diterpene esters such as kahweol palmitate and cafestol palmitate can enhance the enzyme glutathione S-transferase in mice [241] and this in turn may decrease the availability of carcinogens.

Immunotherapy. Immunostimulation that can, in animal models, confer some protection against carcinogenesis includes BCG [242], levamisole [243, 244] and pyran copolymer [245]. A trial of recombinant gamma interferon in patients with carcinomas has also suggested some clinical and histological benefit from interferon [246] but further studies are needed.

The first studies of radioimmunotherapy using radiolabelled anti-ferritin antibodies, or monoclonal antibodies directed against antigens on head and neck carcinoma cells have shown promise against xenografts in nude mice [247–249].

Photodynamic therapy. Photodynamic therapy using haematoporphyrins is effective in animal models [250] and has been used to treat head and neck cancers [251–253] and premalignant lesions in man [254].

Photodynamic therapy (PDT) involves using a specific wavelength of light to activate a photosensitising drug that is retained in the lesion. This produces a photochemical reaction resulting in the generation of reactive products such as singlet oxygen, that damage tissue. PDT appears effective in the management of superficial epithelial lesions, though one study showed 2 recurrences of leukoplakia or erythroplakia within 12 months out of 11 patients with field cancerisation treated with PDT [254]. However, at the present time, there is the major

disadvantage of skin photosensitivity for about 6 weeks after administration of the photosensitiser.

Gene therapy. Patients with head and neck cancer (including oral carcinoma) are more susceptible to chromosome damage when their cells are exposed to mutagens [255], and there are a number of genetic changes now described in oral carcinoma [256]. Synthetic antisense oligonucleotides complementary to the start codons of human papillomavirus (HPV) type 18 E6 and E7 genes can significantly inhibit growth *in vitro* of oral carcinoma cell lines [257, 258].

There are as yet no trials in oral potentially malignant lesions aimed at correcting genetic changes or enhancing the immune response by gene therapy but the whole potential field is well reviewed elsewhere [259].

GENERAL COMMENTS

Whichever form of medical treatment is selected for potentially malignant oral lesions such as some leukoplakias, it is clear that the patient should be counselled to stop or reduce habits such as use of alcohol and tobacco, and to improve the diet. They must be reviewed at least at 6-monthly intervals and advised to seek advice earlier should there be any detectable change in the lesion [45].

Chemopreventive agents do show promise and have recently been extensively discussed [205]. Isotretinoin is effective but at high doses is toxic. Beta-carotene is less toxic but less effective. Newer agents such as fenretinide may be better. Vitamin A is active but it is doubtful whether the data from use in a probably vitamin A deficient population can necessarily be extrapolated to others. Vitamin E may be of benefit. The major drawback for most current agents, however, is the recurrence of lesions when treatment is discontinued.

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