roughly the same extent and stage in the two groups. TF was used in both groups but all in the retinoid group received TF, as against only one in the non-retinoid group. Also the adjunct topical treatment differed, together with the mode of prednisone administration. In spite of these differences, we feel our data should receive attention due to the striking differences in the results of treatment.

Complete remission, including resolution of palpable lymph-nodes, was found in most patients in the retinoid treated group, while only a partial remission was obtained in patients treated with BCP alone, and all of these patients have now succumbed.

Due to the other differences in treatment schedules already mentioned, we dare not at present to attribute the good therapeutic results to retinoids alone. It is our opinion, however, that the addition of retinoids was the most significant difference in treatment between the groups. Our experience has been that PUVA and nitrogen mustard are of equal efficacy (3), and TF has so far shown only insignificant differences in survival rates in MR (6). Further and more easily compared studies on retinoids in MF are necessary.

ACKNOWLEDGEMENTS

This work was supported by the Danish Cancer Society, the Norwegian Cancer Society, the Swedish Cancer Society and the Edvard Welander Foundation.

REFERENCES

1. Elias, P. & Williams, M.: Retinoids, cancer and the skin. Arch Dermatol *117:* 160, 1981.
2. Hogan, B.: Epithelial cancer, differentiation and vitamin A Nature *277:* 261, 1979.
3. Molin, L., Thomsen, K., Volden, G., Groth, O., Fischer, T., Nordentoft, A. & Zachariae, H.: Aspects of the treatment of mycosis fungoides. Cutis *25:* 155, 1980.
4. Sporn, M. & Newton, D.: Chemoprevention of cancer with retinoids. Fed Proc *38:* 2528, 1980.
5. Zachariae, H., Ellegaard, J., Grunnet, E. & Thestrup-Pedersen, K.: Transfer factor in mycosis fungoides: Three years experience. Dermatologica *160:* 1, 1980.
6. Zachariae, H., Grunnet, E., Thestrup-Pedersen, K. & Thomsen, K.: Transfer factor in mycosis fungoides. Proc Soc XI Ann Meeting Scand Soc Immunol, June 1980.

Effect on Oral Leukoplakia of Reducing or Ceasing Tobacco Smoking

B. Roed-Petersen

Department of Oral Medicine and Oral Surgery, University Hospital, Rigshospitalet, Tagensvej 18, DK-2200 Copenhagen, Denmark

Received June 9, 1981

Abstract. Oral leukoplakia patients who were smokers were asked to give up their smoking habits. It was found that leukoplakias present in persons with smoking habits might be reversible, when the smoking habit was reduced or given up. Leukoplakias which were not reversible could possibly be of the same idiopathic type as leukoplakias in non-smokers.

Key words: Oral; Leukoplakia; Tobacco

Oral leukoplakia is a precancerous lesion (1, 2, 3, 5, 7, 9) which has a statistically significant association with tobacco use, either in the form of tobacco chewing or tobacco use, either in the form of tobacco chewing or tobacco smoking (3, 7, 8). This is indicated by observations showing that there is a larger proportion of tobacco users among patients with oral leukoplakia than in the normal population. Furthermore, by undertaking a multivariate analysis on one such set of data it has been shown that the high male–female ratio for oral leukoplakia is secondary to differences in smoking habits among males and females (7).

It has also been reported that oral leukoplakias were reversible after tobacco smoking had ceased (9, 10), and/or local irritants were removed (1), but the effect of stopping smoking was not examined separately (1, 9, 10). The present study was initiated to examine whether reducing or ceasing to smoke tobacco would by itself result in a decrease in or disappearance of oral leukoplakia.

MATERIAL AND METHODS

In the present study oral leukoplakia was defined as a white patch, not less than 5 mm across, which could not be removed by rubbing, and which could not be ascribed to any other diagnosable disease. The definition did not carry any histological connotation (5). The definition is compatible with that suggested in 1978 by the WHO Col-

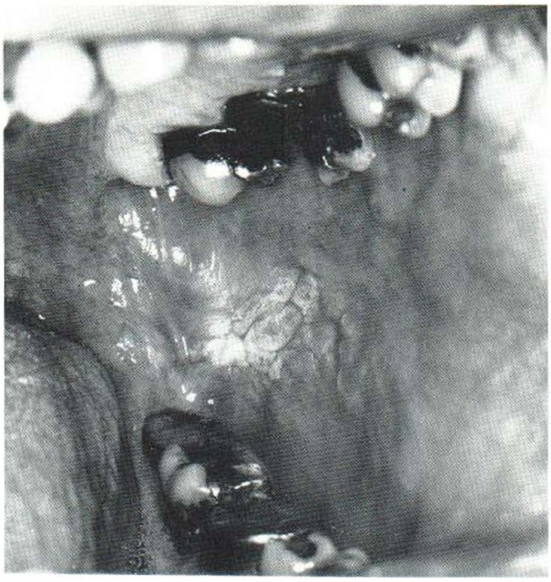

Fig. 1. Leukoplakia of left buccal mucosa in a 60-year-old man smoking 75 g of pipe tobacco per week.

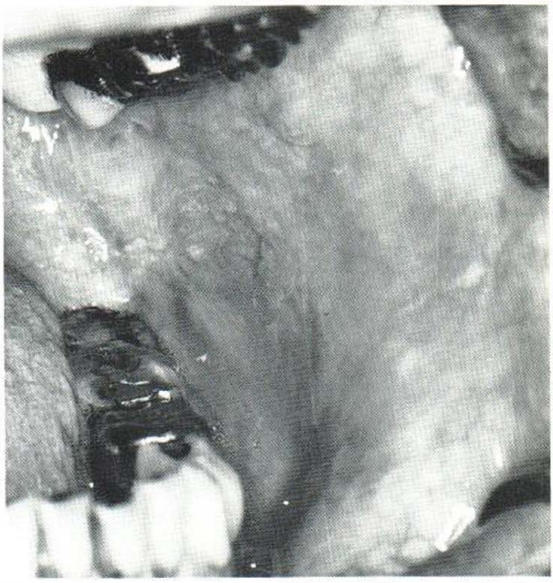

Fig. 2. After reduction to one-third the daily amount of tobacco there is regression but persistence of the leukoplakia at the 3-month control.

laboration Centre for Oral Precancerous Lesions (11). The criteria for inclusion in the study of oral leukoplakias and the details of registration have been reported earlier, (6, 8).

Over a 3-year period new leukoplakia patients who were smokers were asked to give up their smoking habit. A total of 138 patients—63 females and 75 males—responded to the advice. The patients were followed once a month for the ensuing 3 months, and those who were prepared to remain non-smokers were registered one year later. Colour photographs were taken at the first examination and at follow-up visits to record changes (Figs. 1 and 2).

The patients were grouped according to the degree of tobacco abstinence, namely reduction to less than half the normal consumption for 3 months (32 patients), non-smokers for 3 months (70 patients) or non-smoking for one year, i.e. permanent non-smoking (36 patients).

In the statistical analysis Fisher's non-parametric exact test was used, and in larger contingency tables a χ^2-test with Yates' correction.

RESULTS AND COMMENTS

Table 1 shows the distribution and the degree of compliance of the patients in giving up smoking. Among males 30.7% came in the low-compliance group of 3 months' reduction, against 14.3% of the females. In the intermediate group of 3 months' abstinence there was the same proportion, 50%, for both females and males. Among females as many as 34.9% gave up smoking permanently as compared with 18.7% of males. The male and female distributions differed statistically, significantly, $p=0.02$ Subdivision by sex of habit and response of oral mucosa resulted in small numbers and statistical tests were not significant. However, while relative frequencies of lesional behaviour at 3 months' reduction was the same among females and males, there was a trend that in females the relative frequency of the group of unchanged lesions after 3 months' abstinence and after one year's abstinence was twice as large as the corresponding male group. Thus females accounted for three-fourths of the group of lesions which were unchanged after one year of permanent abstinence from tobacco smoking.

In Fig. 3 the data for females and males have been combined. Application of a 3×3 χ^2 test to the corresponding table yields $p=0.0001$. As both regression and disappearance signify reversibility, these two groups have been combined in the black columns which illustrate that after 3 months' reduction of smoking, 56% of leukoplakias disappeared or regressed. In the group abstaining completely this percentage had increased to 63 and reached a peak value of 78% in the group who ceased smoking permanently.

In the present study reduction of the daily tobacco consumption to less than half the normal was

Table I. *Distribution of females and males with oral leukoplakia according to compliance in giving up daily smoking*

Sex	Three months' reduction		Three months' abstinence		Permanent abstinence		Total	
	No.	Row-%	No.	Row-%	No.	Row-%	No.	Row-%
Females	9	14.3	32	50.8	22	34.9	63	100.0
Males	23	30.7	38	50.6	14	18.7	75	100.0
Both sexes	32	23.2	70	50.7	36	26.1	138	100.0

associated with disappearance of leukoplakias in 2 patients (6.3 %). A reduction of smoking, therefore, is of less clinical significance when the treatment is aimed at total disappearance of the leukoplakias. Over the same time span of 3 months, quitting smoking was far more effective, increasing the number of total disappearances to 19 (27.1 %), while the combined group of regression and disappearance increased from 56 to 63 %.

As the percentage of disappearance increased, the group which decreased was not only the group with regression, but also the group of unchanged status. Thus, some lesions which were irreversible at one level were apparently reversible when the dose of the irritant was diminished. As a greater percentage of lesions thus regressed when the antitobacco schedule was intensified, any leukoplakia left alone without smoke for a sufficiently long period might eventually disappear. Alternatively

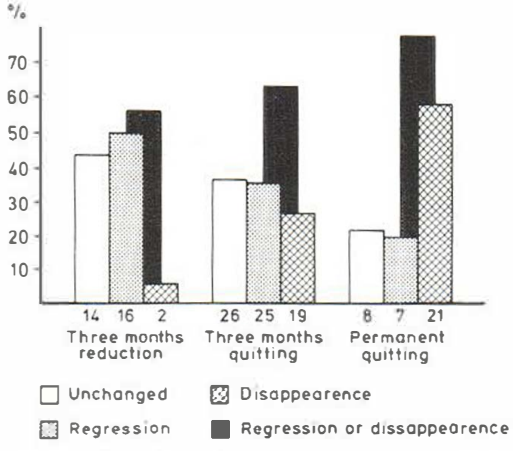

Fig. 3. Effect of reducing or ceasing tobacco smoking on oral leukoplakia in females and males originally smoking daily. The vertical axis presents the % of patients in any of the three groups. Absolute numbers are given along the horizontal axis.

the results might be read to mean that beyond a certain point lesions are no longer reversible even in the case of tobacco abstinence, as some lesions remained unchanged after as much as one year without tobacco. However, neither of these two hypotheses takes account of those oral leukoplakias which are found in persons who have never smoked.

A hypothesis encompassing leukoplakias both in smokers and in non-smokers might be developed along the following lines: Leukoplakias in non-smokers are idiopathic, which however, merely signifies that they are caused by factors so far not identified. As these unknown aetiologic factors must affect smokers, too, a certain percentage of smokers would consequently not be helped by a reduction in or abstinence from smoking.

In a parallel project, oral leukoplakia tissue was transplanted to subcutaneous sites in nude mice, which is a most effective way to ensure that there is no smoke-contact. All of the leukoplakias which lost keratinization came from smokers, whereas none of the leukoplakias from non-smokers lost keratin (4). Thus the direct clinical evidence and the results in animals are mutually compatible.

Further research is in progress on the particulars of the role of smoking habits in the aetiology of oral leukoplakias during the development of oral carcinoma. However, at this stage it may be concluded that when the suspected etiologic agent is removed, the lesion disappears in a considerable number of cases, which was to be demonstrated. Furthermore, as oral leukoplakia as a precancerous lesion can be eliminated by ceasing smoking this is a first-choice measure for primary cancer prevention.

ACKNOWLEDGEMENTS

The study was supported by the Danish Medical Research Council, grants no. 512-15043 and 512-20124. The report

was finalized during grant appointments to The Royal Dental College of Copenhagen and to The Danish Cancer Registry, the latter by grant no. 93/80 from the Danish Cancer Society. Computer time was made available free of charge by Northern Europe University Computing Center, Technical University of Denmark.

REFERENCES

1. Bánóczy, J.: Follow-up studies in oral leukoplakia. J Maxillofac Surg *5:* 69, 1977.
2. Einhorn, J. & Wersäll, J.: Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. Cancer *20:* 2189, 1967.
3. Gupta, P. C. Mehta, F. S., Daftary, D. K., Pindborg, J. J., Bhonsle, R. B., Jalnawalla, P. N., Sinor, P. N., Pitkar, V. K., Murti, P. R., Irani, R. R., Shak, H. T., Kadam, P. M., Iyer, K. S. S., Iyer, M. M., Hedge, A. K., Chandrashekar, G. K., Schroff, B. C., Sahiar, B. E. & Mehta, M. N.: Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. Community Dent Oral Epidemiol *8:* 287, 1980.
4. Holmstrup, P., Dabelsteen, E. & Roed-Petersen, B.: Oral leukoplakia transplanted to nude mice. Scand J Dent Res. In press.
5. Pindborg, J. J., Jølst, O., Renstrup, G. & Roed-Petersen, B.: Studies in oral leukoplakia: A preliminary report on the period prevalence of malignant transformation in leukoplakia based on a follow-up study of 248 patients. J Am Dent Assoc *76:* 767, 1968.
6. Roed-Petersen, B. & Renstrup, G.: A topographical classification of the oral mucosa suitable for electronic data processing. Its application to 560 leukoplakias. Acta Odontol Scand *27:* 681, 1969.
7. Roed-Petersen, B., Gupta, P. C., Pindborg, J. J. & Singh, B.: Association between oral leukoplakia and sex, age and tobacco habits. Bull WHO *47:* 13, 1972.
8. Roed-Petersen, B. & Pindborg, J. J.: A study of Danish snuff-induced oral leukoplakias. J Oral Pathol *2:* 301, 1973.
9. Silverman, S. Jr & Rozen, R. D.: Observations of the clinical characteristics and natural history of oral leukoplakia. J Am Dent Assoc *76:* 772, 1968.
10. Sugár, L. & Bánóczy, J.: Follow-up studies in oral leukoplakia. Bull WHO *41:* 289, 1969.
11. WHO Collaborating Centre For Oral Precancerous Lesions: Definition of leukoplakia and related lesions: An aid to studies on oral precancer. Oral Surg *46:* 518, 1978.

Inhibited Proliferation of Human Scleroderma Skin Fibroblasts and Rheumatoid Synovial Cells with Griseofulvin *in vitro*

G. C. Priestley and J. C. Brown[1]

Department of Dermatology, University of Edinburgh, Edinburgh, Scotland

Received August 7, 1981

Abstract. Griseofulvin at 2–17 μg/ml *in vitro* inhibited the proliferation of scleroderma skin fibroblasts and rheumatoid synovial cells. The inhibition was concentration-dependent, with little difference between the two types of cells. Mean ID_{50} values from the four strains of each group were 9.2 for fibroblasts and 9.5 for synovial cells. The results show that griseofulvin at therapeutic concentrations can have a direct effect on the growth of cells cultured from diseased human connective tissues.

Key words: Griseofulvin; Skin fibroblasts; Scleroderma; Rheumatoid arthritis

We have shown that the antifungal antibiotic griseofulvin inhibits proliferation, glycosaminoglycans (GAG) secretion and protein synthesis in fibroblasts grown from infant foreskin (8). These are characteristic actions of anti-inflammatory drugs, in agreement with previous reports of anti-inflammatory activity for griseofulvin (9), and are of interest in relation to griseofulvin's suggested clinical use in several connective tissue diseases. Because the behaviour of infant genital skin may differ from diseased adult skin on other sites or from other connective tissues, we have now examined the effect of griseofulvin on the proliferation of scleroderma skin fibroblasts and rheumatoid synovial cells in culture.

METHODS

Derivation of four strains of scleroderma skin fibroblasts (SD 3, 6, 9 and 10) and four strains of rheumatoid synovial cells (RA 1, 2, 5 and 6) has been reported elsewhere (7). Cultures were maintained at 37°C in Dulbecco-Eagle medium containing 10% foetal calf serum, 4 mm glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin (all from Gibco-Europe, Paisley, Scotland) with refeeding on alternate days. Cells were in passages 6–12.

[1] *Present address:* Inveresk Research International, Invereskgate, Musielburgh, EH21 7UB, Scotland.