

Follow-up Studies in Oral Leukoplakia

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Of the precancerous conditions of the mouth, leukoplakia is the most common, and it was considered likely that the long-term follow-up of patients would yield valuable information for the control and treatment of the condition.

A study of the histories of 324 patients, in whom leukoplakia had been diagnosed sometime during the previous 23 years, showed that there was a relationship between smoking and the frequency of leukoplakia. Alcohol, mechanical irritants and electric potential difference in the mouth were also important etiological factors, particularly in combination. Many of the cases with mild symptoms improved when the etiological agent was removed.

The cases were classified into groups according to whether there were signs of keratinized mucosa, verrucous proliferations or ulcerated white lesions. The more severe cases more frequently developed carcinomas and were treated by surgery.

Leukoplakia is the most frequent precancerous state of the mouth and the observation of a large number of patients may yield information that is valuable for the study of the carcinogenetic process. It can be done in two ways:

(1) Analysis of the results of a single examination carried out on patients with leukoplakia and determination of the rate of associated oral carcinoma (Fasske, Hahn, Morgenroth & Themann, 1958; Renstrup, 1958; Winiker & Blanck, 1961; Shafer & Waldron, 1961; Pindborg, Renstrup, Poulsen & Silverman, 1963).

(2) Following up the case-histories of patients with leukoplakia for a long period and determining the number of cases that eventually turned malignant. Such examinations were performed by Sturgis & Lund (1934), Weisberger (1957), Sugár & Bánóczy (1959), Skach, Svoboda & Kubát (1960), Mela & Mongini (1966), Einhorn & Wersäll (1967) and by Pindborg, Jolst, Renstrup & Roed-Petersen (1968).

In the present report we shall give an account of our experiences between 1945 and 1968 in following up patients with leukoplakia.

At the Clinic of Maxillo-Facial Surgery and Dentistry in Budapest, 535 patients with leukoplakia

were examined between 1945 and 1968. The follow-up examinations were begun in 1956 and have been repeated 4 times since. In this paper we give an account of the fifth follow-up examination, performed in 1968. All patients with leukoplakia, including those already cured, were requested to appear at the examination. In the course of 1968 we were able to examine 324 patients. A total of 88 new leukoplakia patients, who were registered in the year of the follow-up, were not called for further examination and 123 patients failed to report; of these 15 are known to have died of other diseases, but we have no knowledge of the remaining 108 patients.

An accurate record was kept of every patient, including the anamnesis and clinical state at the time of admittance, and relevant etiological factors such as tobacco and alcohol consumption, and occurrence of mechanical irritation or syphilis. If different kinds of metals were present in the mouth, the electric potential difference observable in the mouth was measured (Inovay & Bánóczy, 1961); in some cases the serum cholesterol level was also determined as hypercholesterolaemia may be a predisposing factor in oral leukoplakia (Thoma, 1954). A cytological examination was made in each case and blood-counts, fungi tests and biopsies were done in those cases in which they were indicated by the clinical picture. The treatment given and subsequent changes were also recorded.

The object of our investigation was to determine:

(1) whether there was a correlation between those

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etiological factors considered and the clinical appearance of leukoplakia;

(2) which method of treatment proved most effective in the long run; and

(3) the percentage of malignant tumours that developed and the type of leukoplakia from which they originated.

In our investigations the term "leukoplakia" was used in a clinical sense to mean a white patch on the oral mucosa that could not be scraped off and could not be classified as any other type of disease. We have distinguished 3 clinical types:

Type I. Keratinized mucosa—leukoplakia simplex

Type II. Verrucous proliferations—leukoplakia verrucosa

Type III. Ulcerated white lesions—leukoplakia erosiva

RESULTS

The distribution by age and sex at the first examination is shown in Table 1. About three-quarters of our patients were men, as was the case in our previous investigations (Sugár & Bánóczy, 1959). The proportion of patients with leukoplakia increased in both sexes after their fortieth year, and 359 patients of a total of 535 belonged to the over-50 age-group.

TABLE 1
DISTRIBUTION BY AGE AND SEX OF PATIENTS WITH LEUKOPLAKIA AT THEIR INITIAL EXAMINATION

Age-group (years)	Male	Female	Total
21-30	11	5	16
31-40	44	15	59
41-50	75	26	101
51-60	124	38	162
61-70	102	32	134
≥71	42	21	63
Total	398	137	535

Our patients had known of their ailment for between 1 and 31 years before the follow-up examination. In many cases they probably had the disease for a longer period as often the leukoplakia had

caused no complaint and was first observed by the patient's dentist. Even so it was surprising to find in our material (Table 2) the relatively high number of cases, 96 of the 324 patients examined, in which leukoplakia had been present for over 10 years, and in 10 cases for over 20 years.

TABLE 2
NUMBER OF YEARS SINCE FIRST DIAGNOSIS OF LEUKOPLAKIA AT THE TIME OF THE FOLLOW-UP SURVEY OF 1968

Period (years)	Male	Female	Total
>1	2	—	2
1-4	58	19	77
5-10	116	33	149
11-19	53	32	85
≥20	7	4	11
Total	236	88	324

At the initial examination in 63% of our cases the lesions were located in the commissures or the buccal mucosa. Leukoplakia was considered as being situated in the commissures if it extended from the commissures, in the usual triangle shape, in a width of about 2 cm directed backwards on the mucosa. It was regarded as being buccal if it was situated in the middle of the buccal mucosa in the region of molars along the occlusal line.

Leukoplakias occurred in about 10% of cases on the tongue and in a further 10% on the hard palate: other locations were still less frequent. We have observed leukoplakia in several sites simultaneously in 65 cases. Buccal-commissures leukoplakias usually situated on both sides in a symmetrical fashion we have considered as of one location.

Studying location by sex (Table 3), we have found the commissures to be the most frequent location in men (42%), followed by the buccal mucosa (22%). In women the position was the reverse; 40% were situated on the buccal mucosa and 19% in the commissures. Leukoplakia of the lips was slightly more common in men (7.1%) than women (4.7%). The occurrence of leukoplakias on the tongue was very different in men (6.8%) and women (14%).

The difference between the sexes in respect of the location of the lesions on the buccal mucosa and

TABLE 3
DISTRIBUTION OF LOCATIONS BY SEX

Location	Male (%)	Female (%)
Commissures	42	19
Bucca	22	40
Lips	7.1	4.7
Tongue	6.8	14
Hard palate	8.1	9.3
Soft palate	1.2	1.8
Floor of the mouth	5.7	6.5
Alveolar ridge	7.1	4.7

commissures proved to be significant at a level of 99%. The difference between sexes in respect of the location on the tongue was shown to be significant at a level of 95%. No significant differences were found between other locations.

We investigated the relationships between the occurrence of leukoplakia and smoking, alcohol, mechanical irritants, syphilis, and galvanism. Of the total number of patients, 83% were smokers; in 13% alcohol, in 32% mechanical factors, in 2.5% syphilis and in 2.5% electric potential difference might be considered as inducing agents. In 199 of the 535 cases (37%) several coexistent factors could be established, while in 22 cases (4.1%), 18 of whom

were women, no etiological factors of any kind could be detected.

The serum-cholesterol test, which was carried out in a few cases in the course of laboratory examinations, resulted in a value over 300 mg per 100 ml only once, otherwise the results were within normal limits.

We made cytological tests on 250 patients with clinically diagnosed leukoplakia. In a single test carried out on 200 patients, atypical cells were found in 7 cases (3.5%), and repeated smears over several years from 50 patients produced malignant cells in 4 cases, that is in 8% of the cases.

Biopsies were performed if malignancy was suspected, or if leukoplakia did not subside after 3-4 weeks of treatment. In fact biopsies were made in 167 cases of which the lesion proved to be malignant in 18 instances.

Fungi tests, both smear and culture tests, were done in 75 cases and *Candida albicans* was revealed in 46 of them.

The effectiveness of our methods of treatment can be seen from Table 4. In this table the status observed at the first examination is compared with the status at the last follow-up examination in 1968. The method of treatment was decided upon on the basis of principles laid down in our previous publication (Sugár & Bánóczy, 1959). Most of our patients recovered or improved solely as a result of eliminating etiological factors and, in certain cases, as a result of conservative therapy applied simultaneously. In many instances, however, the process

TABLE 4
RESULTS ACCORDING TO METHODS OF TREATMENT

Method of treatment	Cured	Im- proved	Un- changed	Increase in size	Carci- noma	Total
Elimination of etiological factors unaccompanied by any other treatment	44	24	10	-	-	78
Elimination of etiological factors accompanied by conservative treatment	30	14	14	-	2	60
Elimination of etiological factors accompanied by surgical intervention	59	14	-	1	-	74
Etiological factors remained or the patients did not come for treatment	-	-	49	16	11	76
Conservative treatment; etiological factors unchanged	1	1	6	5	5	18
Surgical intervention; etiological factors unchanged	1	4	7	6	-	18
Total	135	57	86	28	18	324

TABLE 5
RESULTS OF TREATMENT ACCORDING TO THE TYPE OF LEUKOPLAKIA

Type	Cured	Improved	Unchanged	Increase in size	Carcinoma	Total
I	77	24	40	1	—	142
II	52	26	37	14	5	134
III	6	7	9	13	13	48
Total	135	57	86	28	18	324

remained unchanged and no increase in size was observed. The highest rate of recovery was found in the group of patients from whom etiological factors were removed and who were treated surgically. No recovery or improvement was observed in patients who refused to stop smoking or to have their dentures changed, in spite of our warnings. In such cases healing or improvement and immunity from recurrence respectively could rarely be achieved by applying a conservative or surgical treatment.

Considering the effect of treatment on the different types of leukoplakia (Table 5) it may be stated that the proportion of cured and improving cases was the most favourable in those belonging to type I, i.e., those patients with leukoplakia simplex (which according to our classification represents the clinically mildest form). Exacerbation was experienced in only one case in this group, and we have observed no development of carcinoma. In type II, with verrucous proliferations, the proportion of cases cured was lower: the process spread in several instances and carcinoma developed in 5 cases out of 134 (3.7%). With the type III erosive leukoplakias the tendency for recovery was even worse: carcinoma developed in 13 cases out of 48 (27%). Of the total number of cases in our follow-up studies, 5.5% developed into carcinoma.

DISCUSSION

A relationship between smoking and leukoplakia is generally recognized by investigators who have examined similarly large numbers of cases (Mela & Mongini, 1966). Pindborg & Renstrup (1963) noted the histological changes brought about by smoking. On the other hand Fasseke, Hahn, Morgenroth & Themann (1958) did not attribute any great significance to the relationship with smok-

ing and they classified some of their leukoplakia cases into the group of so-called idiopathic leukoplakias. On the strength of our own investigation we consider that smoking is a positive factor in bringing about leukoplakia as:

(1) The majority of our patients (83%) were smokers.¹

(2) In susceptible individuals smoking may cause hyperkeratosis of the oral mucosa that can be observed clinically, cytologically, and histologically.

(3) Leukoplakia in the initial stage subsides when smoking is stopped.

Alcohol, mechanical irritants and electric potential difference are also important and in combination may produce very serious forms of leukoplakia. Syphilis can be regarded, today, as a subordinate factor in this respect.

Considering the methods of treatment, we may regard the elimination of etiological factors as a fundamental principle. If leukoplakia is in its initial stage, it often subsides simply after their elimination.

The epithelial turnover on oral mucosa takes 16–23 days (Meyer, Medak & Weinmann, 1960). If within 3–4 weeks the process does not subside, the implication is that the chronic pathological irritation has caused irreversible changes in the epithelium of the oral mucosa, and that no healthy, non-keratinizing epithelium can form. In such cases we employ surgical treatment. Analysis of the results of our follow-up studies shows that we achieved the best results in the group of patients treated surgically and consequently our approach to the problem has shifted towards radical solutions. If leukoplakia

¹There are no reliable data concerning the precise number of smokers in Hungary, for the purposes of this paper the percentage of smokers in the adult population has been estimated at about 50%.

does not subside in 3-4 weeks, we remove it completely by means of surgical operation; if it is widespread, we attempt to reduce it by means of vitamin A treatment and perform the operation in several stages. A biopsy is always done.

The worst results and the highest numbers of

carcinoma have been found in the erosive group of leukoplakia. Our experience tallies with the observations of Pindborg & Renstrup (1963) who distinguished a "homogeneous" and a "speckled" type of leukoplakia and who noted the development of carcinoma chiefly with the latter type.

RÉSUMÉ

ÉTUDE DE L'ÉVOLUTION DE CAS DE LEUCOPLASIE BUCCALE

Entre 1945 et 1968, on a procédé à la Clinique de chirurgie maxillo-faciale et de stomatologie de Budapest (Hongrie) à l'examen de 535 patients atteints de leucoplasie buccale. Des contrôles de l'évolution ont eu lieu à plusieurs reprises à partir de 1956. Dans le présent article, les auteurs exposent les résultats du cinquième d'entre eux, effectué en 1968, qui a porté sur un total de 324 malades.

L'étude de la répartition par sexe au moment de l'examen initial fait apparaître une proportion de 75% d'hommes parmi les malades. Chez les hommes, les commissures des lèvres (42%), puis la muqueuse buccale (22%) sont le plus fréquemment atteintes; chez les femmes, les localisations principales sont par ordre de fréquence la muqueuse buccale (40%) et les commissures des lèvres (19%).

On s'est attaché au cours de cette étude à mettre en évidence d'éventuels facteurs étiologiques. Ont été ainsi considérés comme facteurs favorisants: le tabac (dans 83% des cas), l'alcool (13%), des facteurs mécaniques (32%), la syphilis (2,5%), et des différences locales de potentiel électrique (2,5%). Dans 199 cas sur 535 (37%), une association entre différentes causes a été décelée; dans 22 cas (4,1%), l'étiologie est restée absolument inconnue.

Le traitement chirurgical, accompagné de la suppression des facteurs étiologiques, a donné les meilleurs résultats. La proportion des guérisons et des améliorations a été la plus forte chez les patients atteints de formes légères (leucoplasie simple, avec kératinisation de la muqueuse). On a observé au total 5,5% de cas d'évolution vers le cancer, ayant pour la plupart pour origine des lésions leucoplasiques ulcérées.

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