

# Reversibility of snuff dippers' lesion in Swedish moist snuff users: a clinical and histologic follow-up study

Åke Larsson<sup>1</sup>, Tony Axéll<sup>2</sup> and  
Gunilla Andersson<sup>2</sup>

Departments of <sup>1</sup>Oral Pathology, <sup>2</sup>Oral  
Surgery and Oral Medicine, Lund University,  
Malmö, Sweden

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The purpose of this study was to assess possible reversibility of oral mucosal changes, associated with the use of Swedish moist snuff, after change of habit. Biopsies from a total material of 252 regular snuff users, 184 using loose snuff and 68 using portion-bag packed snuff, were screened microscopically to identify histopathologic epithelial changes in addition to, or differing from, those generally seen as a result of snuff use. The main basis for selection of these variables were the criteria of epithelial dysplasia as defined by WHO and the eight histologic features, which have been reported to be the most important discriminators to separate cases with leukoplakia that subsequently developed carcinoma, from those that did not. Twenty-nine subjects, 3 showing Degree 2 lesions, 21 Degree 3 lesions and 5 Degree 4 lesions, all of them loose snuff users were identified. All the 29 users were re-examined clinically and histologically after 3-6 months. The rebiopsy was always secured from the same mucosal area as the original biopsy. At follow-up, 20 subjects had either stopped their snuff habit or changed to portion-bags and changed placement of the quid. All of them showed a healthy mucosa at the previous biopsy site and normal tissue in the histologic examination of the rebiopsies. Seven subjects had changed to portion-bags and variably reduced their daily exposure to snuff. At follow-up they presented with less pronounced clinical changes and the rebiopsies showed evidence of reduced epithelial changes. One major conclusion from this study is that tissue changes, clinically as well as histologically, are reversible following cessation of snuff habit. This statement is also valid for such parameters used to define dysplasia which may occasionally occur in snuff dipper's lesion.

Key words: leukoplakia; mouth disease; oral mucosa, pathology; snuff; tobacco, smokeless.

Gunilla Andersson, Department of Oral Surgery and Oral Medicine, Faculty of Odontology, Lund University, S-214 21 Malmö, Sweden.

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It is frequently stated that the habit of snuff dipping is harmful to the oral tissues. The question of whether mucosal changes caused by snuff show histologic features of dysplasia or carcinoma is, however, a matter of dispute. This is because it is not known to what extent the parameters usually used to define dysplasia (1, 2) occur in tissue alterations observed in snuff dippers, often referred to as snuff dippers' lesion. Furthermore, if parameters characteristic of dysplasia are found in snuff dippers' lesion, it is not known whether or not the presence of these parameters is predictive of carcinoma.

This dispute may be due to lack of experimental data or to ill-defined specifications of type of tobacco (3). A complicating factor may be a lack of consensus regarding the criteria, as well as the

use of the term dysplasia. For example, KAUGAR *et al.* (4) equated dysplasia with "pre-malignant lesion" using microscopic features accepted by WHO (1) as the determining criteria. They noted that 90.9% of their selected cases demonstrated "epithelial dysplasia" at the site of tobacco placement. No follow-up data were, however, provided. Conversely, SMITH *et al.* (5) examining 15,000 snuff users, found that none of 157 biopsied patients with clinically detected mucosal change showed signs of dysplasia or carcinoma after 5 years of follow-up. Of these 157 cases, 128 were followed for another 4.5 yr, but no patient showed signs of dysplasia or malignancy (6). SMITH *et al.* (5) concluded that there was no reliable data pointing to the ability of unburned tobacco to cause oral neoplasia. They further

stated that without well-documented clinical studies or experimental evidence, many writers and clinicians seem to accept an association between mouth cancer and long-term snuff use. It seems that this 20-yr-old statement is still valid, at least with respect to the types of snuff consumed by the Swedish community (about 4500 tons a year by about 800,000 individuals). However, it is well recognized that mucosal changes regularly occur in snuff dippers, (7, 8), but our knowledge about the biologic nature or behavior of such changes is limited.

The purpose of the present study was to assess the possible reversibility of lesions after change of habit in cases originally showing some, but not all, of the parameters of dysplasia, by examining follow-up biopsies.

### Material and methods

The original material consisted of biopsies from 252 healthy men with regular use of non-fermented Swedish moist snuff for at least the last 3 months and with no other current tobacco use; 184 used loose snuff and 68 used portion-bags. For a detailed description of the material see ANDERSSON & AXÉLL (7). The histopathology of those biopsies has been generally characterized in a previous publication (8). In short, the biopsies were found to present a fairly consistent pattern of changes. Among the loose snuff users, predominantly "type 1" surface changes were found, featuring non-keratinized swollen surface epithelial cells with or without a chevron-type pattern as well as an accompanying eosinophilic surface layer indicative of the chemical etching effect of the snuff. These changes were sometimes combined with epithelial hyperplasia and an increased mitotic rate, and invariably with connective tissue inflammation. Similar changes could be detected among the users of portion-

bag packed snuff. "Type 2" changes, characterized by a keratinized (rhodamine B positive) surface layer, were more often recorded among portion-bag users than among loose snuff users.

In the present study all the 184 + 68 original biopsies were screened microscopically with the purpose of identifying histopathologic epithelial changes in addition to or differing from those generally seen as a result of snuff use as described above. Twenty-nine subjects, all of them loose snuff users, were identified. The distribution of clinical grading was: 3 cases showed Degree 2 lesions, 21 cases Degree 3 lesions and 5 cases Degree 4 lesions. For detailed information on consumption and clinical grading see Table 1. All the 29 snuff users were re-examined clinically after 3-6 months, following efforts to have them stop, or at least change their habit. The biopsy for microscopic re-evaluation was taken at least 6 months after change of habit and was always secured from the same mucosal area as the original biopsy. As a group for comparison, 5 loose-snuff users were selected based

on a daily consumption of at least 25 g consumed during 12 h or more. For detailed description see Table 1. Sections were stained with H-E, PAS, rhodamine B or Congo Red.

In the microscopic re-examination of the 184 + 68 original biopsies, a group of epithelial changes were identified in some of the biopsies, including various combinations of increased mitotic rate, increased cell density (including "basilar hyperplasia", 8) and loss of cell cohesion. Some other slight changes, including the criteria of epithelial dysplasia as defined by WHO (1), were also observed. In order to determine their significance, an effort was made to assess subjectively the absence or presence of a number of different variables, which have been deemed important in previous, snuff-related studies. The main basis of selection of these variables was the eight histologic features, which KRAMER (9) reported to be the most important discriminators to separate cases with leukoplakia who subsequently developed carcinomas, from those that did not. The parameters KRAMER suggested were used with slight modifications and additions, as follows:

- 1 Abnormal mitoses in the stratum basale and/or spinosum, and/or an overall increased mitotic rate, as defined previously (8).
- 2 Disturbance of polarity of basal cells, in which the long axis of the cells is no longer clearly perpendicular to the basement membrane.
- 3 Nuclear hyperchromatism, with few or groups of cells, mostly basal, staining more intensely than neighboring cells.
- 4 Russell bodies in the lamina propria.
- 5 Enlarged nucleoli.
- 6 Pleomorphism, with variations in cell and nuclear shape.
- 7 Intraepithelial keratinization.
- 8 Loss of epithelial intercellular cohesion, with or without accompanying inflammation.
- 9 Basal cell hyperplasia with an increased thickness of the basal cell layer resulting in "increased density" (8).

In addition to these variables, eosinophil infiltration was recorded, as a possible potent mediator of tissue damage (10) and thereby a possible contributor to loss of intercellular cohesion (p. 8 above). The degree of hyaline change in the lamina propria was also recorded to seek a possible relationship with any of the other variables included in the study. Based on recent reports of possible disturbances of the mitotic process by

Table 1. Age and snuff exposure data of 29 follow-up cases

Group	Accession No.	Age	Consumption			Clinical Degree
			h/day	g/day	Yr	
1	264	57	17	25	30	4
	255	29	10	33.3	10	3
	212	23	5	9.1	8	4
	369	27	11	6.2	6	3
	268	28	14	28.6	10	3
	204	70	14	12.5	8	4
	331	21	8	33.3	3	3
2	209	34	12	40	17.5	4
	216	25	6	14.3	5	3
	284	49	15	16.7	14	3
	287	25	14	25	12	3
	343	34	16	50	17.5	3
	345	26	7	16.7	11	3
	365	21	10	25	3	3
	388	40	10	12.5	12.5	3
	386	32	13	40	11	4
	227	21	10	28.6	8	3
	366	47	12	12.5	25	3
	248	60	15	25	40	3
	291	41	13	33.3	11	3
	314	54	15	25	5	3
	363	42	7	8.3	10	2
	377	30	15	50	15	3
	384	39	15	66.7	24	3
	374	33	8.5	20	3.5	3
3	245	22	3	12.5	3	3
	315	29	11	16.7	11	3
	238	23	10	20	5	2
4	313	48	16	5	25	2
Cases for comparison	226	39	12	25	20	3
	338	51	14	40	7	3
	351	29	14	25	13	3
	229	47	16	25	29	3
	289	58	12	25	12.5	3

Table 2. 29 follow-up cases. Histologic changes defined according to text.

	Accession No.	Increased mitotic rate	Loss of cohesion	Increased cellular density	Eosinophil infiltration
Group 1	264	+	+	+	+
	255	+	+	+	—
	212	+	+	+	+
	369	+	+	+	+
	268	+	+	+	+
	204	+	+	+	+
	331	+	+	+	+
Group 2	209	+	—	+	—
	216	+	—	+	—
	284	+	—	+	—
	287	+	—	+	—
	343	+	—	+	—
	345	+	—	+	—
	365	+	—	+	—
	388	+	—	+	—
	386	+	—	+	—
	227	+	—	+	—
	366	+	—	+	—
	248	+	—	+	—
	291	+	—	+	—
	314	+	—	+	—
	363	+	—	+	—
	377	+	—	+	—
	384	+	—	+	—
	374	+	—	+	—
	245	+	—	+	—
	315	+	—	+	—
Group 3	238	—	—	+	+
Group 4	313	—	+	+	+
Cases for comparison	226	—	—	—	—
	338	—	—	—	—
	351	—	—	—	—
	229	—	—	—	—
	289	—	—	—	—

tobacco treatment (11), binucleate spinous cells were recorded. Biopsies were arbitrarily regarded as positive, if at least two binucleate cells could be found within the confines of any individual rete peg.

### Results

All the 184+68 original biopsies showed some degree of inflammation in the connective tissue. A few (*vide infra*) showed hyaline change, which was Con-

go red/amyloid negative. No cases with binucleate cells, abnormal mitoses, Russell bodies, intraepithelial keratinization or prominent nuclear hyperchromatism could be recorded. All biopsies showed some degree of nuclear enlargement, with visible nucleoli. Only occasionally a case with a slight degree of pleomorphism or some loss of basal cell polarity was observed. The histopathologic findings of 29 loose snuff users exhibiting in their original biopsies some degree of epithelial change in addition to what could be generally observed as a result of snuff use (p. 1-9 above), is summarized in Table 2. Among portion-bag snuff users, no cases showing corresponding changes were found. Based on the findings, we arbitrarily subdivided the 29 loose snuff users into four subgroups for re-biopsy analysis, as follows.

**Group 1** – Seven cases, which all showed a combination of an increased mitotic rate, increased cell density and evidence of loss of cohesion. Six of these showed eosinophils and four had hyaline changes in the lamina propria. Four of them (acc Nos. 264, 255, 212, 369) had given up the snuff habit at follow-up and showed a healthy mucosa at the previous biopsy site and normal tissue in the histologic examination of the re-biopsies (Figs. 1-3). Among these four was the only case (acc No. 264, Fig. 2) exhibiting a clinical Degree 4 lesion in our previous study of the impact of consumption factors (12). Among the remaining three cases, one subject (acc No. 268) had exactly the same habit at the follow-up, again presenting with a clinical Degree 3 lesion and with an un-

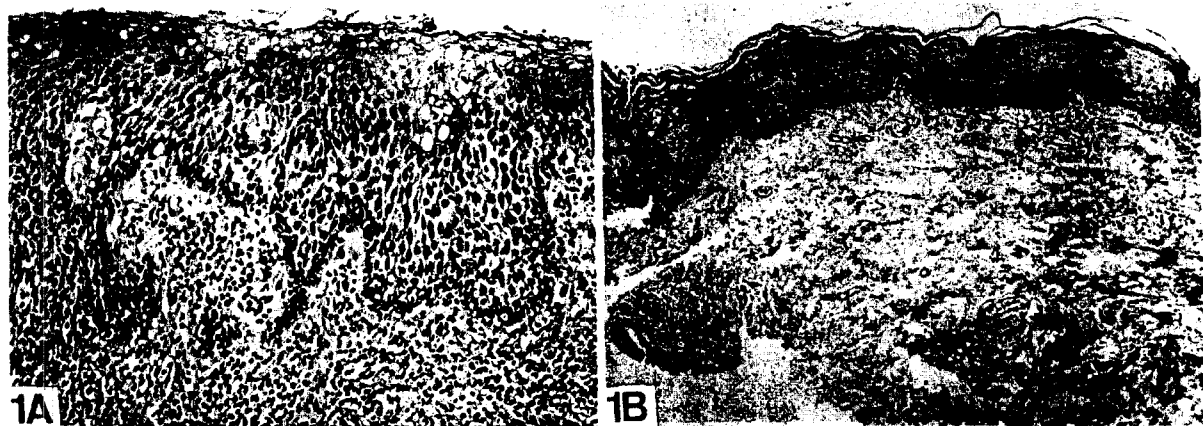


Fig. 1 A, B. (Acc No 212). 22 yr old man with clinical Degree 4 lesion following use of loose snuff (5h daily, 9.1 g a day, 8 yr with regular habit). Original biopsy (A) showing non-keratinized epithelium with irregular rete pegs, combined with inflamed connective tissue. Epithelial surface cells are swollen and necrotic. Loss of cellular cohesion is evident. This biopsy also showed increased mitotic rate, localized areas of basilar hyperplasia and eosinophilic granulocytes. Following stop of snuff habit, rebiopsy taken 1 yr later (6 months after he stopped to use snuff) showed normal epithelium, with only a few inflammatory cells in the connective tissue (B). A:  $\times 140$ . B:  $\times 70$ .

changed histologic picture. Two individuals (acc Nos. 204 and 331) had changed to portion-bags, had reduced their daily consumption (204- 6h/d, 5g/d; 331-sporadical use) and now placed the quid at several different sites. At the follow-up they both had clinical Degree 1 lesions at the original biopsy site. Histologically, inflammation and minor epithelial surface changes were recorded but increased mitotic rate, cell density and cohesion loss was no longer seen.

**Group 2** – Twenty cases with an increased mitotic rate and an increased cell density but without loss of cohesion. None of these had eosinophils or hyaline change in the lamina propria. Eleven of these (acc Nos. 209, 216, 284, 287, 343, 345, 365, 388, 386, 227, 366) had stopped the snuff habit at least three months before the follow-up examination. Clinical-

ly, as well as histologically, they showed a normal mucosa at the site of rebiopsy (Fig. 4). Four subjects (acc nos. 248, 291, 314, 363) had changed to portion-bags and reduced the amount of grams used daily but they exposed the mucosa for the same number of hours as before. They had also changed the placement of the snuff. At the follow-up, one of these (acc No. 248) had a clinical Degree 2 lesion while the other three had Degree 1 lesions at the site where the tobacco was held. However, all four had a normal looking mucosa at the previous biopsy site, which was supported by the histologic analysis. Among the remaining five cases, four had changed their habit to portion-bag packed snuff (acc Nos. 517, 384, 374, 245). They had the same daily exposure time to snuff but had reduced the amount consumed to about one-half.

All four showed clinical Degree 2 lesions at the time of rebiopsy. Histologically, in contrast to the original biopsies, the rebiopsies showed no increased mitotic rate or increased cell density. One individual (acc No. 315) continued to use loose snuff, but he had reduced the daily exposure slightly to 11 g/d during 9 h and placed the snuff at two different sites. At the follow-up he still presented with a clinical Degree 3 lesions although somewhat less marked (thinner). Histologically, in addition to type 1 surface changes, a few mitoses were recorded but no increased cell density.

**Group 3** – One case (acc No. 238) had an increased cell density but without increased mitotic rate or loss of cohesion. This case showed eosinophils and hyaline changes. At the follow-up he had not modified his snuff habit in any

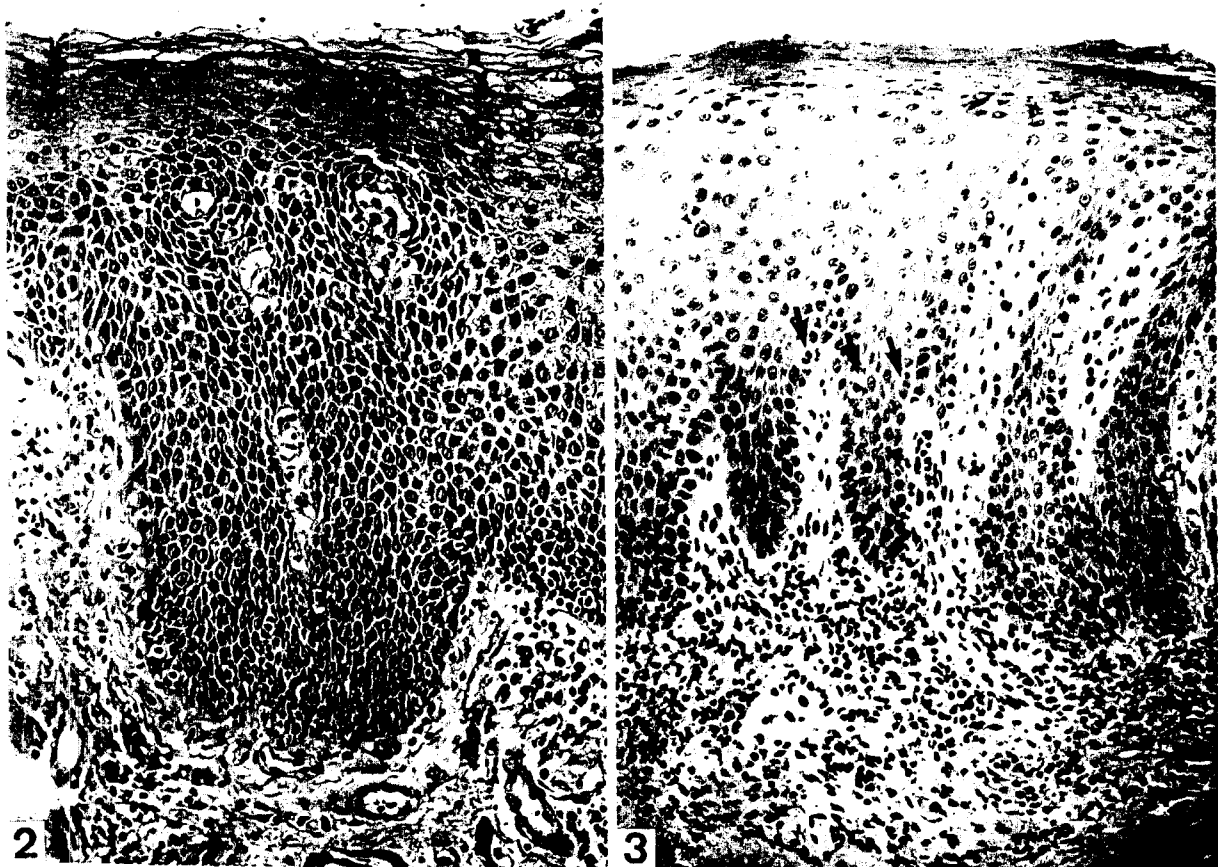


Fig. 2. (Acc No. 264). 57-yr-old man with clinical Degree 4 lesion following use of loose snuff (17 h daily, 25 g a day, 30 yr with regular habit). Original biopsy, showing epithelial hyperplasia with swollen or necrotic surface cells and some connective tissue inflammation. Slight degree of basilar hyperplasia is seen as well as loss of cohesion. This biopsy also showed increased mitotic rate and eosinophilic granulocytes. Following stop of snuff habit, rebiopsy taken 18 months later (6 months after he stopped to use snuff) showed normal tissue, similar to Fig. 1B.  $\times 200$ . Fig. 3. (Acc No. 369). 27-yr-old man with clinical Degree 3 lesion following use of loose snuff (11 h daily, 6.2 g a day, 6 yr with regular habit). Original biopsy, showing epithelium with slightly drop-shaped rete pegs, basilar hyperplasia and necrotic surface zone. Clearly increased mitotic rate was recorded (arrows) as well as evidence of loss of cohesion with eosinophilic granulocytes also within epithelium. Connective tissue is heavily inflamed. Following stop of snuff habit, rebiopsy taken 6 months later (6 months after he stopped to use snuff) showed normal tissue, similar to Fig. 1B.  $\times 200$ .

way and presented with a clinical degree 2 lesion similar to the original examination. The histologic picture was also the same at both occasions.

**Group 4** – One case (acc No. 313) had loss of cohesion and increased cell density but without an increased mitotic rate (Fig. 5A). The original biopsy also showed eosinophils. He stopped his snuff habit and at the follow-up 6 months later, the previously recorded Degree 2 lesion had disappeared and the mucosa looked normal. The rebiopsy also showed normal tissue when examined microscopically (Fig. 5B).

#### Cases for comparison

Three of the five cases showed type 1 surface change, the other two type 2. Three cases (acc Nos. 226, 338, 351) showed normal mucosa, clinically and histologically, at follow-up. They had either discontinued their snuff habit (acc No. 338) or changed to portion-bags and changed the placement of the snuff quid (acc Nos. 226, 351). The two cases showing persistent changes (acc Nos. 229, 289) had only modified their habits slightly.

#### Discussion

In the present study, approximately 10% of all the biopsies, 29 cases from a total material of 184 loose snuff and 68 portion-bag packed snuff users, as described previously by ANDERSSON & AXÉLL (7), exhibited epithelial alterations different from or in addition to what was subjectively found to predo-

minate in such lesions, as previously described (8). The purpose of the present study was to define the possible reversibility after change of habit, of such epithelial alterations. Five "prototype" cases served as rebiopsy controls. For practical purposes, we have been unable to rebiopsy all the remaining cases.

Although the selection of the 29 cases, who exclusively used loose snuff, was based on an initial subjective analysis of the 184+68 biopsies, there was still an empirical foundation for the selection in the sense that it was based on the use of histologic criteria, usually used to assess the presence and degree of dysplasia (1, 2). Following rebiopsies of these 29 cases, we then reapplied a complete set of nine different histological parameters, which closely correspond to those found by KRAMER (9) to be important predictors of subsequent malignancies in cases with oral leukoplakias. Our present findings suggest that snuff dipper's lesion may occasionally show some, but not all, of such histologic changes. These changes include various combinations of an increased mitotic rate, an increased basal cell density and a loss of cell cohesion. With the exception of enlarged nucleoli, which was a more or less constant finding in all the 184+68 biopsies, none of the remaining five parameters could in fact be found in the present material.

Irrespective of the histologic changes originally observed in the biopsies, all those cases in the present study who discontinued completely their snuff habit, were found to exhibit a normal mucosa in their rebiopsies. Thus, we

found reversibility in 20 of the 29 cases. Of the remaining nine cases, seven showed evidence of reduced epithelial changes, associated in all cases with a variably reduced use of the snuff. One major conclusion from this study must therefore be, that the changes we have found to be present in the 29 cases, including also in the five additional cases for comparison, are reversible following cessation of the snuff habit. Among the seven cases showing the most extensive combination of KRAMER's (9) parameters, (our group 1) four returned to normal in the re-biopsy following cessation of snuff use whereas two of the remaining three cases showed reduced changes following reduced daily snuff use and change of product. Since these changes correspond to some of the parameters used to define dysplasia, an additional conclusion must be that the changes do not correspond to "dysplasia" if dysplastic lesions are thought to be irreversible.

There are several previous studies, reporting no (5, 6, 13) or mild to moderate dysplasia in snuff dipper's lesion (4, 14, 15, 16, 17, 18). The majority of these studies lack histologic illustrations. Interestingly, we have found that the few illustrated cases do not show changes which markedly differ from any of those we have observed in the present 29 rebiopsied cases.

An interesting observation in the present study was that seven of the nine cases showing loss of intercellular cohesion also exhibited eosinophilic infiltration, and that seven of the eight cases showing eosinophils also had evidence

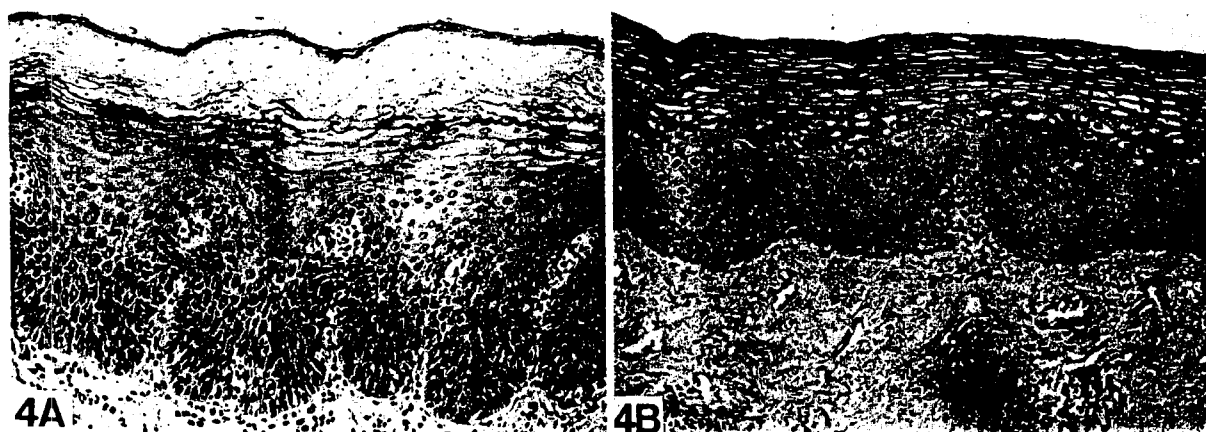


Fig. 4A, B. (Acc No. 209). 34-yr-old man with clinical Degree 4 lesion following use of loose snuff (12 h daily, 40 g a day, 17.5 yr with regular habit). Original biopsy (A) showing epithelium with rounded, slightly drop-shaped rete pegs and thick surface layer of vacuolated cells ("Type 1 change"), accompanied by necrotic surface zone and also some connective tissue inflammation. Increased mitotic rate was recorded (arrows) as well as some basilar hyperplasia but no obvious loss of cell cohesion and no eosinophilic granulocytes. Following stop of snuff habit, rebiopsy taken 2 yr later (18 months after he stopped to use snuff, but he did not allow rebiopsy until 2 yr after the original one) showed normal tissue (B).  $\times 140$ .

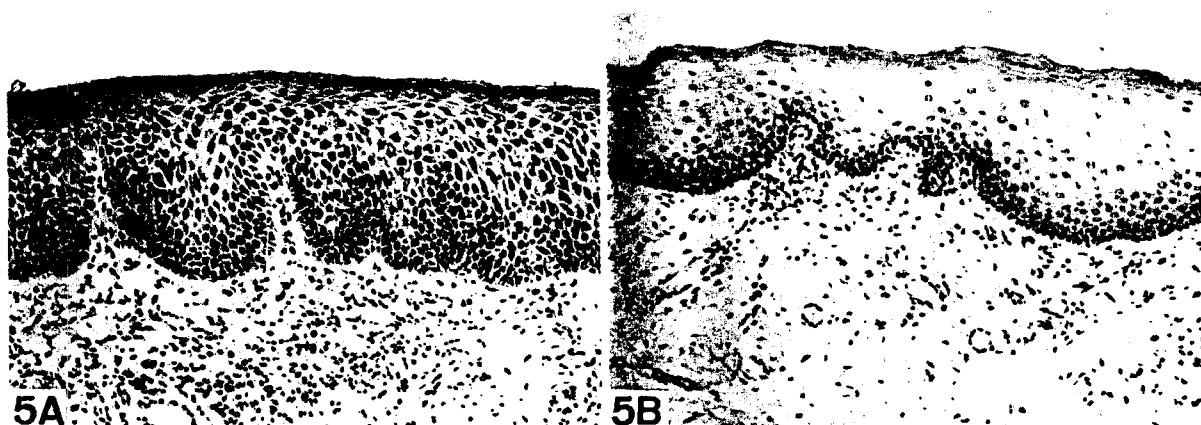


Fig. 5 A, B. (Acc No. 313). 48-yr-old man with clinical Degree 2 lesion following use of loose snuff (16 h daily, 5 g a day, 25 yr with regular habit). Original biopsy (A), showing somewhat atrophic epithelium with flattened surface cells, evidence of loss of cellular cohesion and of basilar hyperplasia. Eosinophilic granulocytes were also found. Isolated mitoses were recorded but mitotic rate was not found to be increased. Following stop of snuff habit, rebiopsy taken 6 months later (6 months after he stopped to use snuff) showed normal tissue, with only few inflammatory cells (B),  $\times 140$ .

of loss of cohesion. Further, none of the 20 cases of our Group 2, with no evidence of loss of cohesion, showed any eosinophils. Eosinophils have been previously reported in snuff dipper's lesions (13) but possible functional connection with loss of cell cohesion has not been emphasised. The occasional infiltration of human tumors by eosinophils has been noted and discussed for nearly 100 yr (19) but their prognostic significance has been questioned (20). The findings by SILBERSTEIN *et al.* (21) suggest that eosinophil infiltration and possible cytotoxic function in tumors may be indirectly mediated via IL-2. We suggest therefore that eosinophil infiltration in snuff dipper's lesion is a secondary phenomenon, as a consequence of the non-specific inflammation invariably found in these lesions, and that the concomitant loss of cell cohesion may be a result of eosinophil cytotoxic functions.

A better understanding of the biologic nature of the histologic changes occurring in snuff dipper's lesion is highly desirable. If there are snuff dipper's lesions that are non-reversible, it is obvious that they must look different from what we have reported in the 29 selected cases, with clearly reversible changes. Furthermore, it follows from a definition of dysplasia as "a disturbance in the maturation of the cellular layers of the stratified squamous epithelium" (2, 5, 22) that the disturbed maturation must occur from the basal cell layers and upwards, since this is the direction of differentiation in oral squamous epi-

thelium. By the same necessity, the direct effects caused by placing snuff on the mucosal surface must take place from the surface layers and downwards. From this simplistic view it may be argued, that morphologic evidence of a disturbed maturation, i.e. "dysplasia", must be mixed together in a snuff dipper's lesion with the morphologic changes caused by the direct chemical, etching effects of the snuff. Consequently, the crucial question is to what extent changes corresponding to disturbed maturation can be histologically identified among the direct changes inevitably caused by the snuff.

Based also on observations in the present study, we are inclined to believe that dysplasia has not been present in any of the 29 cases. This is further supported by the fact that in spite of a large number of oral biopsies per year submitted from all over Sweden, we have never recorded a carcinoma developing in a patient with a pre-existing snuff dipper's lesion. The changes recorded in this study are reversible and we, therefore, interpret them as reactive. They represent a well-defined set of changes following defined habits of using defined types of snuff. To avoid oversimplified statements, evaluation of future studies in any given population will decisively depend upon whether tissue changes have been correlated with type of snuff, e.g. dry or moist, pH-values and package form and to what extent the degree of reversibility correlates to detailed histologic changes.

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