Focal epithelial hyperplasia in Sweden

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Axéll, T., Hammarström, L. & Larsson, Å. Focal epithelial hyperplasia in Sweden. *Acta Odontol. Scand.* 1981, 39, 201 - 208

A prevalence of 0.11 % of focal epithelial hyperplasia (FEH) was found among 20,333 adult Swedes. There was no sex difference, the lesion was most prevalent in age groups above 45 years and the lesion was most frequent on the tongue. The frequency of FEH in 15,132 consecutive routine biopsies was 0.26 %. Four FEH-cells were ultracstruturally examined. They exhibited a clear cytoplasm with scattered ribosomes, a peripheral condensation of tonofilaments, a central aggregation of chromatin clumps with loss of nuclear membrane and an accumulation of desmosome fragments. No viral particles could be identified in these FEH-cells.

Key-words: Papova virus; epidemiology; electron microscopy

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Since 1965, when Archard et al. (1) reported on the finding of focal epithelial hyperplasia (FEH) among American Indian children, the lesion has been recognized in several populations throughout the world (14). In contrast to remarkably high prevalences (32–34 %) in American Indians (19) and Greenlandic Eskimos (15), only very low figures or isolated cases have been reported in Caucasian populations. Praetorius-Clausen (13) found one case among 322 Caucasian Danes living in Greenland, i. e. a prevalence of 0.3 %. Notably he did not find one single case of FEH among 3,000 conscript Danish soliders living in Denmark. In a study of oral mucosal lesions in an adult Swedish population, Axéll (2) found a surprisingly high prevalence. Isolated cases have also been reported from Sweden. Bergenholtz (3) described two cases of 'multiple polypous hyperplasias' and Thomsson & Hammarström (20) found FEH in five out of nine members in a Turkish family living in Sweden.

From this brief review it appears that FEH is rarely reported among Caucasians in spite of the fact that it may be as common as e.g. papilloma and mucocele and more common than lipoma in the oral cavity (2). The purpose of the present study was to present detailed epidemiologic data from Axéll (2) of FEH in a general Swedish Caucasian population and further to analyze the frequency and some of the pathologic characteristics of FEH in an oral pathology biopsy service in Sweden.

Received for publication, February 10, 1981

MATERIAL AND METHODS

Epidemiology

This study was carried out in the County of Uppsala, located centrally in Sweden. In collaboration with a health screening organization, the population aged 15 years or above, totalling 30,118 people, were summoned for examination. 20,333 individuals (10,036 males, 10,297 females) with a mean age of 43.0 years (males 42.6, females 43.4 years) were examined. The outline of this investigation has been reported previously (2, pp. 11–36).

All lesions suspected of FEH were photographed in colour and biopsies were secured from most of these lesions. The clinical types of FEH in the present study were subgrouped according to the following criteria:

Type 1. Circumscribed sessile, soft rounded and nodular elevation(s) with a colour like that of the adjoining mucosa (Fig. 1).
Type 2. Well demarcated, soft, slightly elevated papule(s) with a flat, whitish surface or with a colour like that of the adjoining mucosa (Fig. 2). Both types showed a partly irregular boundary between the affected and unaffected mucosa (Figs. 1,2).

Information on tobacco habits was collected on pretyped standardized forms through interviews. Prevalences were calculated through weighing procedures where due consideration was taken to findings and frequencies of participation in different demographic groups. Calculation of the difference between sexes was carried out by means of a chi-square-test with Yate's correction. For details see Axéll (2).

Pathology

A total of 15,132 consequtive biopsies from the files of the Department of Oral Pathology, Malmö, from the period 1974–1980, were analysed for the frequency of FEH. All cases classified as FEH according to the WHO-classification (24) were reexamined and reclassified according to the histopathologic criteria of FEH as defined by Praetorius-Clausen (12). Three cases were routinely prepared for electron microscopy. All cases from the biopsy files were tabulated according to age, sex, biopsy location and geographic distribution.

RESULT

Epidemiology

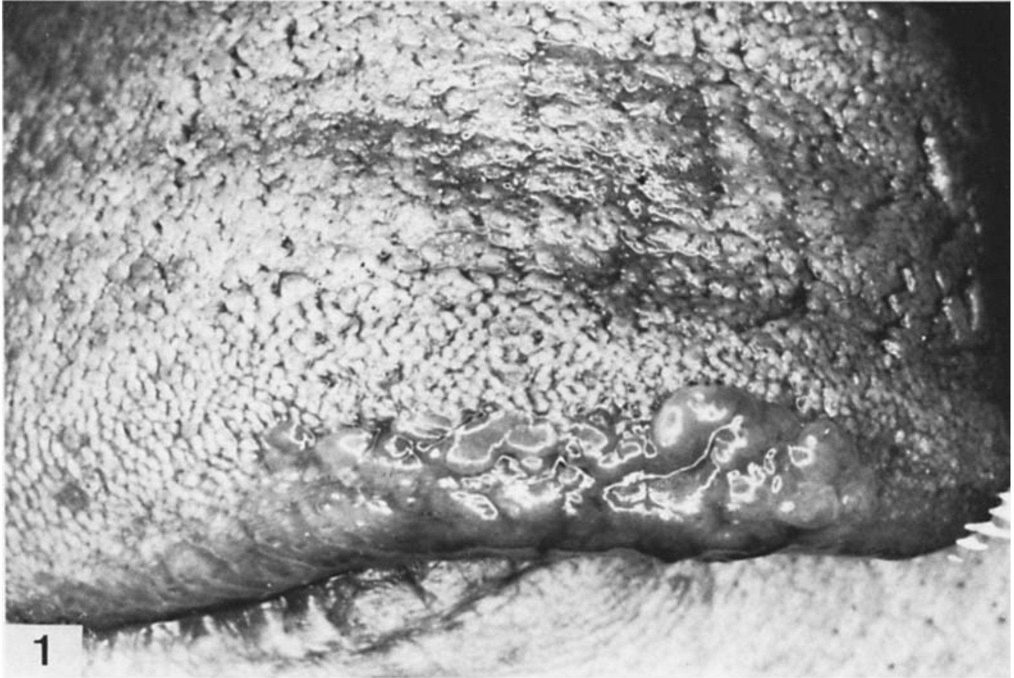
A total of 17 cases of FEH were registered, corresponding to a prevalence of 0.11 %. The prevalences for males and females were 0.09 % and 0.12 %, respectively (Table 1). The diagnoses were established on clinical criteria in 3 cases and on combined clinical and histological criteria in 14 cases.

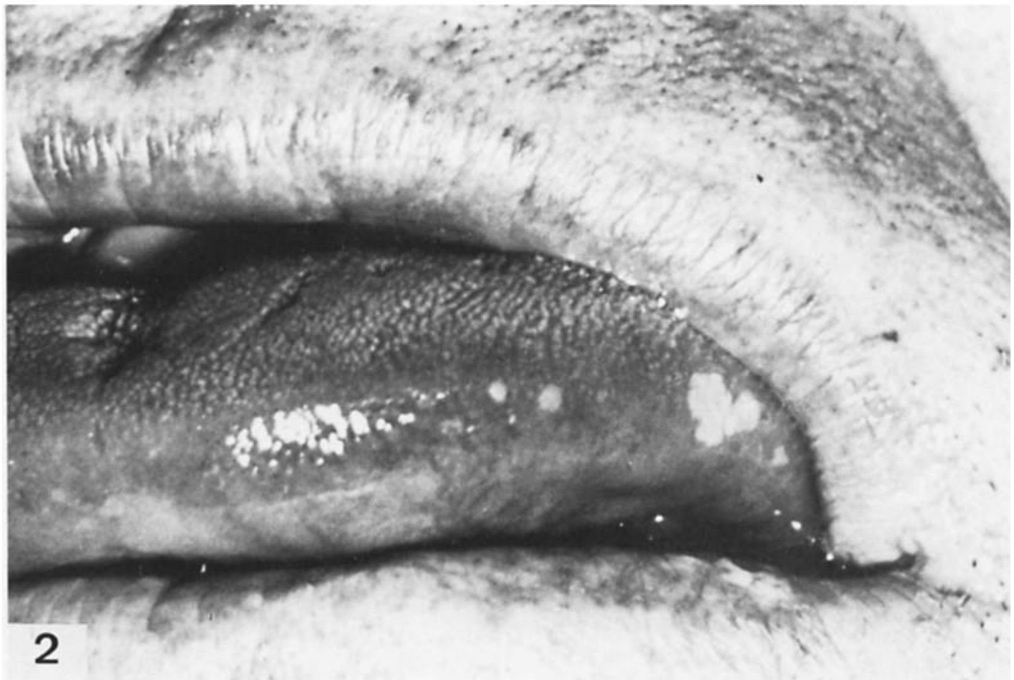
All individuals with FEH were 45 years of age or older, except for a 16-year-old boy, whose father also suffered from the lesion (Table 1). The lesions were found in Caucasians only,

Table 1. *Age and sex distribution of 17 individuals with FEH*

Age, years	Males, number	Females, number	Total, number	
15–44	1	–	1	
45–54	2	3	5	
55–64	3	–	3	
65–74	3	2	5	
⩾ 75	1	2	3	
Total	10	7	17	
Prevalence percent	0.09	0.12	0.11	n.s.
Average age, years	57.5	63.0	59.8	
Range of age, years	16–79	47–79	16–79	

n.s. = not significant at the 5 % level.





Figs. 1 – 2. Illustrating the two clinical types of FEH, type 1 and 2 respectively, at the margin of the tongue.

and with no geographic predilection. Thus, lesions were registered in individuals living in six different parishes representing both urban, suburban and rural regions.

In total, 44 lesions of FEH were registered among the 17 cases, i.e. 2.6 lesions on an average. The highest number found in one person was six, and the lowest was one. 32 of the lesions were classified as type 1 and 12 lesions as type 2. 11 patients showed type 1 and four showed type 2 lesions. Two patients had lesions of both types.

The most frequent location of FEH was the tongue, especially the margins. In a few cases the lower labial mucosa and the labial commissures were involved (Table 2).

Six persons reported on various daily tobacco habits, while 11 denied any tobacco consumption.

Pathology

A total of 41 cases (= 0.26 % of the total biopsy referrals) were histopathologically confirmed as FEH. The clinical distribution was not examined in detail, but in 19 cases (46 %) the biopsy originated from the tongue. The sex distribution was 18 males and 23 females, with a mean age of 54.6 and 52.7 years, respectively. Biopsies are submitted to the Department from all parts of Sweden. The distribution of the 41 cases of FEH showed no predilection for any part of the country.

The light microscopic appearance of FEH is illustrated in Fig. 3. One of the prominent features of FEH is the presence at various levels of the epithelium of ballooning cells showing mitosis-like aberrations, 'FEH-cells' (Fig. 4). Four FEH-cells from lesions of a 12 year-old girl showing clinical signs of active growth of her FEH, could be sectioned for ultrastructural examination (Figs. 5–8). They all showed a clear cytoplasm with scattered ribosomes, a peripheral condensation of tonofilaments and a central aggregation of clumps of chromatin, with no definable nuclear envelope. Mitochondria and membrane-delimited dense granules were also identified, but endoplasmic reticulum was inconspicious. The FEH-cells were attached to neighbouring cells by desmosomes. In addition, accumulation of desmosome fragments was a prominent finding among the tonofilament bundles. No virus particles similar to those described in several previous reports of FEH could be identified in the FEH-cells.

DISCUSSION

Previously, FEH has been considered extremely rare in Caucasians, with only isolated cases reported (11). The prevalence found in the present study, 0.11 %, is remarkably high, but the validity of this figure is supported by the

Table 2. *Distribution as regards location of totally 44 FEH lesions*

Location	Number (%) of lesions in affected location	Number (%) of patients with lesions in affected location
Tongue	40 (91 %)	15(88.2 %)
Right margin	16	12
Left margin	15	8
Apex	8	7
Dorsum	1	1
Lower labial mucosa	2(4.5 %)	1 (5.9 %)
Labial commissures	2(4.5 %)	2(11.8 %)

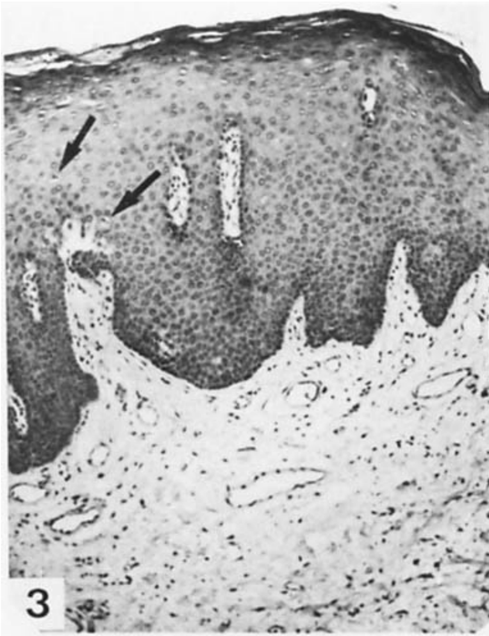
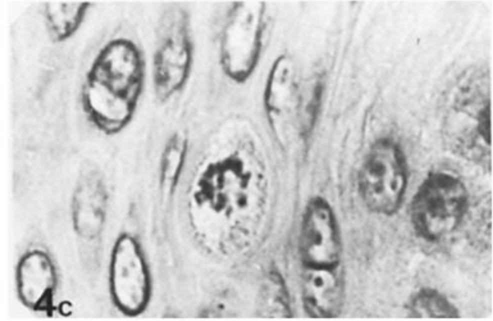
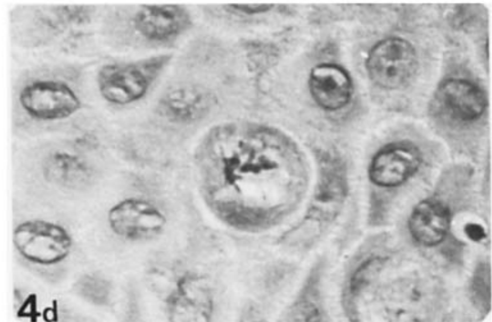
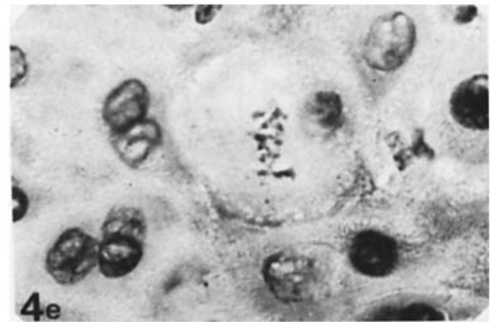
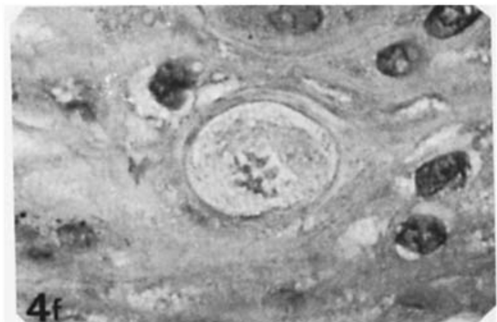


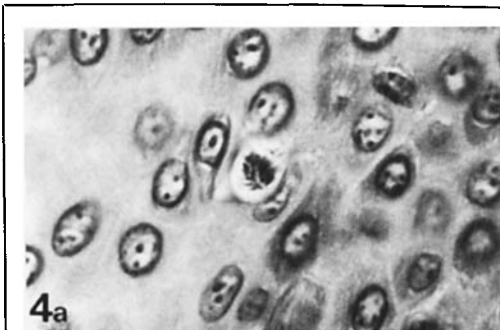
Fig. 3. Low magnification light micrograph illustrating the histologic appearance of FEH. The connective tissue is vascular, with an insignificant degree of inflammation. The epithelium is thickened, with rete pegs extending downwards and also laterally, forming anastomosing bridges. There is an increased cellularity in the epithelium, where «FEH-cells» (cf Fig. 4a-f) are a characteristic finding (arrows). X 120











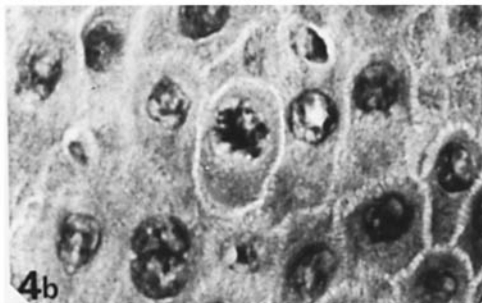


Fig. 4 a-f. High magnification light micrographs showing the detailed appearance of six different FEH-cells. These are enlarged epithelial cells, with their nuclear chromatin condensed in a mitosis-like pattern. The central part of the cell is clear whereas the periphery is occupied by a rim of eosinophilic cytoplasm. X 700

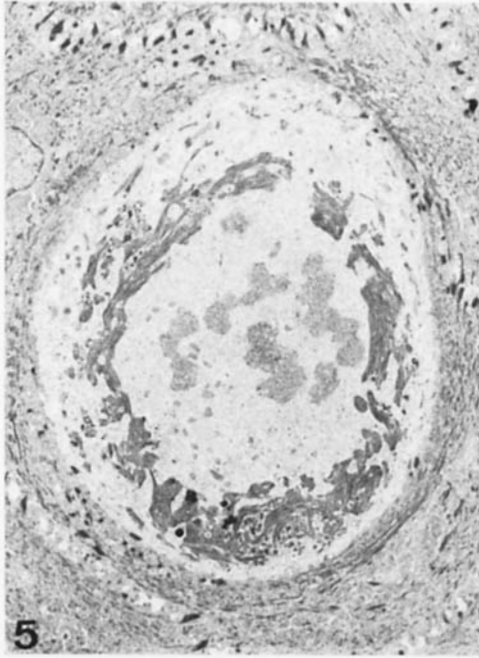


Fig. 5. Ultrastructurally, the FEH-cell appears as a round, clear cell, lacking the density of normal neighbouring epithelial cells. At the periphery, a prominent rim of eletron-dense material is seen (cf fig. 6). In the centre, the nucleus is completely replaced by irregularly formed collections of moderately electron-dense material, cf Fig. 7. X 3200

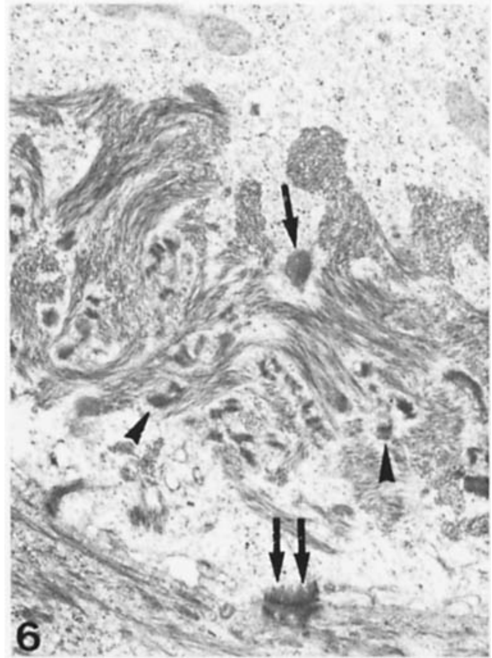


Fig. 6. The peripheral rim of dense material in the cytoplasm of the FEH-cell (cf fig. 5). consists of bundles of tonofilaments. Among these are desmosome fragments (arrow heads) shown at greater detail in fig. 8. Free ribosomes and a few vesicles (single arrow) are seen in the cytoplasm. The cell is attached to neighbouring epithelial cells by desmosome contacts (double arrow). X 17,700

Figs. 5 – 8 are electron micrographs showing some of the ultrastructural features of the FEH-cell, cf fig. 4 a-f. All sections were uranyl-lead contrasted.

rather high proportion of FEH in the biopsy material (0.26 %). Probably there has been a previous lack of recognition as regards the clinical and histological characteristics of the lesion, but other explanations are possible.

A genetic factor has been suggested in the etiology of FEH since the lesion is by far most prevalent among American Indians and Greenlandic Eskimos (14). Isolated cases of FEH found among Turkish immigrants in Sweden (20) and also in Germany (10) point at a racial factor possibly explaining the high prevalence in our study. However, all 17 cases in the present epidemiologic study were Caucasians. Further, based on our biopsy referral data, Lapps, ethnically related to Eskimos and living only in northern Sweden, did not seem to contribute significantly to the frequency of FEH.

A familial occurrence of FEH in families has often been reported (1, 7, 15, 16, 18, 21). Some evidence of this was also found in the present study, since the probability of finding two cases of a low prevalent lesion like FEH by chance in one family is extremely low. Even though the familial occurrence may support the idea of a genetic factor in the etiology of FEH, it may also support the concept that FEH could be associated with a weakly contagious infection, as is also suggested by van Wyk (22).

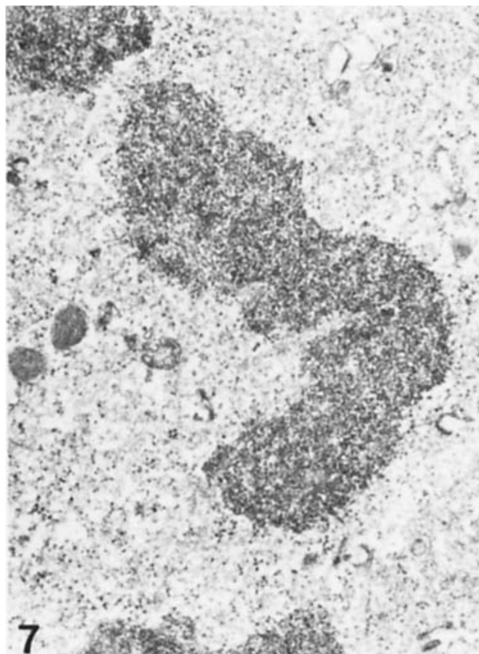


Fig. 7. Higher magnification of the irregular masses of material seen in the centre of the FEH-cell, cf fig. 5. The density and morphology of this material is similar to that of nuclear chromatin. No traces of a nuclear envelope can be seen around these masses. X 20,100

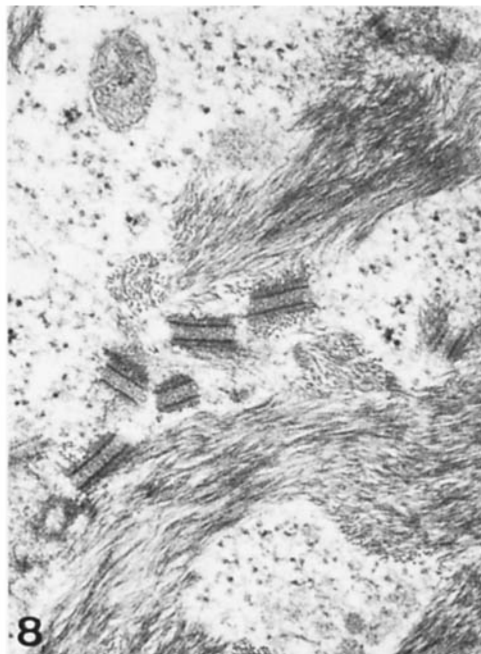


Fig. 8. Detail of tonofilament bundles shown in fig. 6, with desmosome fragments interspersed among the fibrils. The significance of these desmosomes is not known. X 43,300

No sex predisposition was observed in the present investigation. This is in agreement with findings by Praetorius-Clausen et al. (16). Previously, FEH has been frequently found in children (1, 7, 19, 21). However, as pointed out by Praetorius-Clausen et al. (16) this may partially be explained by the fact that very few persons more than 18 years of age have been examined. In their Greenlandic study of 460 Eskimos they found the highest prevalence in the age groups above 30 years, a finding supported in the present study. These findings also contradict the assumption set forth by Gómez et al. (7). that FEH disappears in adults.

The intraoral location of FEH is a matter of controversy. Thus, Gómez et al. (7) consider the tongue to be an infrequent site as compared to other oral sites. In contrast, Praetorius-Clausen et al. (16) found FEH most frequently located to the tongue, a finding also supported by the present results. The lesion was most frequently located to the margins and to the apex of the tongue. Thus, it seems that local irritation from teeth may be an etiologic factor in FEH. Irritation from electro-galvanic currents between amalgam fillings (3) has also been suggested. In the present study irritation from tobacco habits does not seem to be a significant etiologic factor.

Based on ultrastructural observations of FEH in man (8, 17, 23) and also in laboratory animals (5, 9), there is strong evidence that FEH is a virus-induced disease. Papova virus-like particles have been demonstrated mainly within the nuclei of affected epithelial

cells. van Wyk et al. (23) described the conceivable sequence of changes of the virus-infected epithelial cells. We have made no detailed search for virus in the present study, but based on relevant literature and also on our own observations, it seems that the FEH-cell is not the major host of virus particles in FEH. This cell is one of the most characteristic histopathologic features of FEH, but the natural course of the cell is unknown. Our observations indicate that the hallmarks of the FEH-cell are the peripheral condensation of tonofilaments accompanied by accumulations of desmosome fragments and central aggregation of chromatin clumps. The ultrastructural appearance is not that of a lytic cell, and the cell should not be confused with the clear cells invariably observed in FEH (4, 5). Its features are similar to those described in early stages of bizarre and arrested mitotic division (6, 23). Since the FEH-cells tend to appear at any level of the affected epithelium, we suggest that the cytomorphologic changes of the cell represent a unique reaction to the virus infection, separate from that reported in the virus-particle-containing cells.

Acknowledgement. The epidemiologic part of this project was supported by a grant from the Swedish Tobacco Company.

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