Graefe's Arch Clin Exp Ophthalmol (1992) 230:340–347

Graefe's Archive
for Clinical and Experimental
Ophthalmology

Conjunctival cytology in asymptomatic wearers of soft contact lenses

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Received December 15, 1990 / Accepted August 19, 1991

Abstract. Conjunctival epithelium was systematically investigated with impression cytology in clinically asymptomatic wearers of soft contact lenses who had been using their lenses for several years. Severe abnormalities were observed, which had so far only been seen in diseases of the ocular surface mainly in dry eye syndromes. All patients showed evidence of squamous metaplasia with distinctly enlarged, flattened cells without evidence of keratinization. They also showed frequent nuclear abnormalities, primarily a high percentage of snakelike-appearing condensations of nuclear chromatin (snakes). The goblet cell density observed was relatively low. Snakes were for the first time detected outside the known localization (upper bulbar conjunctiva, 12 o'clock position) and could be demonstrated throughout the whole bulbar conjunctival epithelium. It is suggested that the changes observed are due to chronic mechanical irritation by the contact lens, as indicated by their topographical distribution and as proven by their reversibility after omission of contact lens wear.

Introduction

The majority of the well known and often reported complications of contact lens (CL) wear are subjective symptoms and more or less easily distinguishable macroscopic changes of the ocular surface (vascular injection, corneal and/or conjunctival edema, neovascularization of the superficial marginal plexus of the cornea [4] or inflammation of various etiology, etc.). The reasons for that are multiple and range from poor lens fitting, allergic reactions to lens material or lens care products, to prolonged wearing time, or insufficient lens hygiene.

Since there has been some indication in literature [8, 10] of conjunctival epithelial changes in apparently asymptomatic contact lens wearers, the present investigation was established in order systematically to explore the conjunctival epithelium of long-term wearers of soft hydrogel contact lenses. These patients were neither symptomatic nor did they have macroscopic changes or alterations detectable by slit-lamp examination. Wearers of soft contact lenses were chosen because this lens type is widely used and usually shows good wearing results due to the optimized quality of material nowadays.

For the investigation of asymptomatic patients, impression cytology (IC) provides simple and noninvasive means of evaluating the conjunctival epithelium. It is a kind of exfoliative cytology in which a mostly one-layered epithelial cell sheet is collected on a small piece of Millipore filter. Since the lateral cell adhesion remains unaltered [15, 20] and hence the topographic orientation of the cells is preserved, it not only allows qualitative examination of single cells but also quantitative assessment of the epithelial status. It has therefore been used to investigate the conjunctival epithelium in several functional disorders of the ocular surface.

First, after being introduced by Egbert et al. [5] in 1977 as a "biopsy" (sometimes obtaining cells a few layers deep), it was used as a tool for evaluation of the ocular mucus system. Goblet cells (GC) were investigated in dry-eye disorders [5] or their mucus products in normal eyes [3], while Nelson and Wright [25] performed counts of goblet cell density (GCD, an important criterion of conjunctival integrity [29]) and reported a reduction in all investigated surface diseases. Thatcher et al. [33], who first used the term "impression cytology," applied a similar technique for leukocyte counts and microorganism detection in immunological and infectious conjunctival diseases. The development of a "grading system" by Nelson et al. [27] based on epithelial cell size, nucleocytoplasmic (N/C) ratio, nuclear morphology and GCD (later extended by Tseng [35] to rate the epithelial keratinization in addition) allowed systematic and comparable investigation of ocular surface diseases. Squamous metaplasia was then reported in various dry eye disorders, inflammations and immunological reactions, and keratinization was confirmed in most of these. IC was used further for nondestructive, repeat-

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ed follow-ups of epithelial morphology as, for example, after therapeutic irradiation [19].

Peculiar snakelike condensations ('snakes') of nuclear chromatin were first detected by Marner [24] in 1980 in keratoconjunctivitis sicca (KCS) and Sjögren's syndrome. These were suspected of being an artifact, but were later confirmed by others [8, 23], even with different methods (routine histological sections [18]) and in other diseases (following irradiation [19]). Although the number of snakes seems to be generally correlated with the severity of disease [23, 24], their significance is still unclear.

Materials and methods

Specimens were obtained of 14 younger people, mostly long-time wearers of soft contact lenses who volunteered in a CL study [14, 16]. They had a mean CL wearing time of approximately 5 years [about 13 h daily at the time of investigation (Table 1)]. Two of them had had a lens-free interval, which had lasted until half a year before the beginning of this investigation. All patients had normal eyes except for minor refractive disorders, which were corrected by the lenses. No pathological findings were seen in routine ophthalmological examination (slit lamp inspection of the cornea and conjunctiva with additional fluorescein staining to exclude epithelial erosions), and no ocular complaints were reported. Dry eye was excluded by Schirmer's test and a tear film break-up time test.

For evaluation of the normal appearance of conjunctival epithelium in IC, specimens were obtained from 14 control persons who were chosen to be comparable in age and sex (Table 1) with the CL wearers. These were wearers of glasses who also showed only minor refractive abnormalities without objective or subjective conjunctival findings.

IC was carried out in a slightly modified procedure compared with other authors, which required neither special impression equipment [7, 18, 19, 24] nor special processing equipment [35].

Millipore cellulose acetate filters (Millipore VSWP 0.025 µm) were cut into pieces approximately 3–4 × 15 mm in size, held with a forceps on a small side, brought into contact with the conjunctival epithelium, and gently applied with the rounded end of a glass rod for a few seconds. The rougher side of the two different faces of the filter paper was attached to the ocular surface.

The preferred localization for IC was the upper bulbar conjunctiva at 12 o'clock, 3–5 mm distal to the limbus. Additional specimens were obtained from some patients (six) at 6:00, 3:00, and 9:00 at the same distance to the limbus and from peripheral areas of the bulbar conjunctiva at approximately 10–15 mm from the limbus.

After removal, each piece of filter paper was mounted (cells facing up), selectively at one end with two-sided adhesive tape to a microscope glass slide; the end selected was the one that had been touched by the forceps. This technique allowed easy handling in the steps following and simplified treatment of large amounts of specimens. The specimens were then fixed by air drying and ready for further electron [15, 17] or light microscopic (LM) treatment.

In this LM study the staining procedure by Tseng [35], using PAS, hematoxilin, eosin Y and orange G, was applied. After being air dried again, the specimens were rinsed with xylol, which rendered transparent the primarily opaque filter paper and allowed the attached cells to be examined with light microscopy. Finally, coverslips were placed over the specimens with Eukitt and they were then photodocumented.

Assessment of the cytological situation was performed, recording cell size, N/C ratio, morphological changes of the nucleus, GCD, and the occurrence of keratinization.

The different cell sizes were determined by classifying the closely related (see in results) changes of the N/C ratio into five groups: N/C ratio of 1:1 = normal-sized cells [n], 1:2–1:3 = little enlarged cells [l], 1:4–1:6 = medium enlarged cells [m], 1:8 = large cells [g] and an N/C ratio above 1:8 = very large cells [xg]. Cells size 'm' and larger were regarded as squamous. Cells of N/C ratio 1:8 were easily detectable by their relatively high diameter in connection with a nucleus of normal appearance. Squamous cells larger than 1:8 were identified by their pyknotic nuclei. Cell classification into these groups was done dependent on the dominant cell size in the sample.

The number of snakelike nuclear chromatin condensations was differentiated into six groups according to the relative percentage in the cell layers of the specimens obtained, ranging from 0 to more than 75%: group [0] = no snakes; [I] = 1–10%; (II) = 11–25%; [III] = 26–50%; [IV] = 51–75%; [V] = > 75%. The grade of cytological changes was obtained in a semiquantitative classification procedure, giving valid and reproducible results.

The GCD was examined by counting GCs or their mucus imprints on the filter paper. This was done on colorslide reproductions of an enlargement of 25 times using a dissection microscope.

Table 1. Data on contact lens (CL) wearers and controls

	Contact lens wearers	Controls
Sex: M	7	8
F	7	6
AGE	28.71 (±4.29) years	24.07 (±4.43) years
CL: Wearing time	5.25 (±3.24) years	∅
Daily wear	13.57 (±1.74) h	∅
Cell size	Increased	Normal
N/C Ratio	Average size ca. 1:5	ca. 1:1
Cell shape	Polygonal and with squamous deformation	Round
Nucleus: Morphology	Often changed (pyknosis, rhexis, binucleated, segmented)	Roundish
Chromatin	Frequently inhomogeneous	Homogeneous distribution
Snakes	13/14 (in about 25% of cells at 12 o'clock)	1/14 (in less than 10% of cells at 12 o'clock)
Goblet cell density	134/mm² (±95)	170/mm² (±56)

Results

Normal conjunctival epithelium

The IC picture showed a mostly one-layered sheet of densely adjacent cells of equal size and roundish shape with a relatively large nucleus and a small cytoplasmic rim (normal N/C ratio 1:1; Fig. 1). The nuclei stained homogeneously dark blue with fine dark chromatin particles. The cytoplasm was homogeneously light blue (Figs. 1, 2a). One patient in this control group surprisingly showed snakelike nuclear condensations in a few (less than 10%) of the cells at the upper bulbar conjunctiva, while the two former contact lens wearers, with a lens-free interval of about 2 years, had a completely normal cytology.

Frequent GCs could be detected only in areas with more than one cell layer adhering to the filter (Fig. 2a, b). They were somewhat larger than the other epithelial cells, unequally distributed in small groups and easily detectable by the intense pink colour resulting from the PAS-positive reaction of the content of their secretory granules. Areas with monolayered cell sheets (Fig. 1) and cell-free parts of the filter (Fig. 4a) usually only showed imprints of GC secretions, but no GCs itself (Fig. 4a, b). Occasionally mucus could be seen in the form of heaps of different size (Fig. 4c) and mucus threads (Fig. 4d) usually interconnecting heaps or GCs.

Changes of epithelial cytology in contact lens wearers cell size, N/C ratio. All patients showed markedly increased cell sizes and N/C ratios. In the upper bulbar conjunctiva there were mostly no normal-sized cells left, and enlarged cells of various N/C ratios dominated the imprints (Fig. 3).

The up to double increase in cell diameter was primarily related to enlargement of the cytoplasm, while the nucleus was usually still normal in size. Therefore, cell enlargement necessarily resulted in a corresponding increase in the N/C ratio. Since the increase in cell diameter and N/C ratio proved to be directly connected, the cell size relative to normal cells was determined just by assessing the actual N/C ratio, which served as an indicator for size. No absolute measurement (in micrometers) was necessary using this technique. Speaking strictly mathematically, the N/C ratio is *de*creasing in this process ($1:8 = 0.125 < 1:1 = 1$), but since these changes are the result of an increase in cell diameter, the term chosen seems to be adequate.

In cells that were more than double the normal diameter (i.e., an N/C ratio > 1:8), the nucleus usually showed pyknotic degeneration, so beyond this point, size and N/C ratio did not correlate any longer, but in these clearly squamous cells, no further size assessment was necessary.

An increased cell diameter was generally accompanied by flattening of the cell shape and may have been primarily caused by this morphological change. Furthermore, enlarged cells frequently occurred in loosened populations (Fig. 3), presumably resulting from a decrease in intercellular adherence, and showed an alteration in cell shape, e.g., spindle form (Fig. 5a). Cells that were more than two times the normal diameter often lay isolated on the filter, rarely in small clusters, and frequently showed rolling of the cell margin (Fig. 5b, arrows). Morphological deformations finally resulted in cytolysis with loss of cellular integrity (Fig. 6a). Cells were rarely observed that had an intact cytoplasm above 3 times the normal diameter.

In the upper bulbar conjunctiva, year-long contact lens wearers showed a mean cell size of about N/C ratio 1:5 ('m'), which is fairly enlarged in comparison with normal cells (N/C ratio 1:1) and significantly different (exact p-value < 0.0001) from controls. None of the CL wearers had a predominantly normal cell size at this localization, and one showed predominantly large cells ('g', N/C ratio 1:8) (Fig. 9). Even patients with less increased dominating cell size (l, l+m) had patches with large squamous cells.

There was no evidence of keratinization of the enlarged and deformed cells, as was verified by the absence of light microscopically detectable keratohyalin granules. On the contrary, these cells sometimes showed an increase in cytoplasm transparency.

Nuclear changes. Apart from the indicated changes in cell size, shape and intercellular adherence, there were frequently also nuclear abnormalities.

There were roundish inhomogeneities of the chromatin material (Fig. 8b, arrows) mainly in smaller cells, while larger ones sometimes showed cloddish condensa-

Fig. 1. Normal conjunctival epithelium as seen by impression cytology (×280)

Fig. 2a, b. Interspersed whole goblet cells in multilayered normal cell zones showing PAS positive reaction; **a** ×280; **b** ×690

Fig. 3. Enlarged cells (mainly sizes 'm' and 'g') with nuclear alterations (*arrows*, binucleated cells; *arrowhead*, large nucleus; ×280)

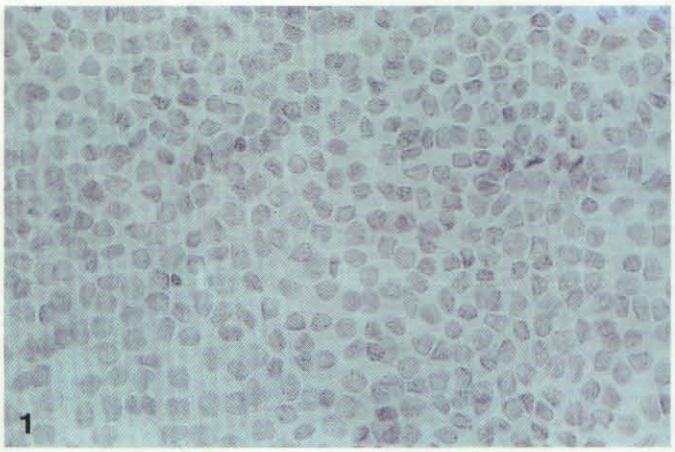
Fig. 4a–d. Different aspects of the mucus in normal conjunctiva (always showing PAS positive reaction). At cell monolayers and cell free parts of the filter paper only impressions of goblet cell mucus adhere: **a** ×280; **b** ×690. In addition, mucus in heaps, with foamy appearance, containing cells or single nuclei, occasionally granulocytes (**c** ×110) and mucus threads with adherent epithelial cells (**d** ×110)

Fig. 5a, b. Enlarged cells showing different alterations of their shape. **a** Spindle shape in moderately enlarged cells (×280); **b** folding (*arrows*) of flattened isolated cell bodies and nuclear pyknosis in very large squamous cells (×280)

Fig. 6a, b. Enlarged cells with alteration of cytoplasm and nucleus. **a** Highly enlarged cells showing cytolysis and nuclear pyknosis (*arrowheads*, plasma fragments), sometimes followed by nuclear fragmentation (Karyorrhexis) (*arrow*) (×690); **b** Binucleated flattened cell (×690)

Fig. 7. High percentage (>75%) of snakelike nuclei, even in moderately enlarged or normal-sized cells (×280)

Fig. 8a–c. Nuclear abnormalities (×690): **a** Snakelike chromatin with intact nuclear envelope (various stages of nuclear condensation), in addition, different stages of segmentation of condensed nuclei (*BS*, beginning; CS, complete); **b** vacuolelike inhomogeneities (*arrows*); **c** cloddish nuclear condensation (*arrow*)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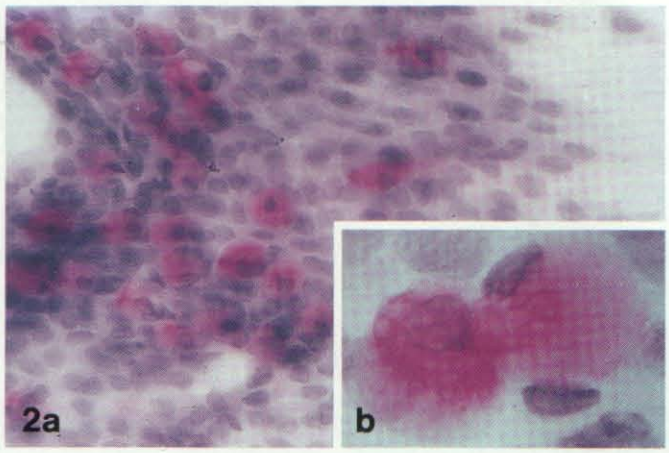
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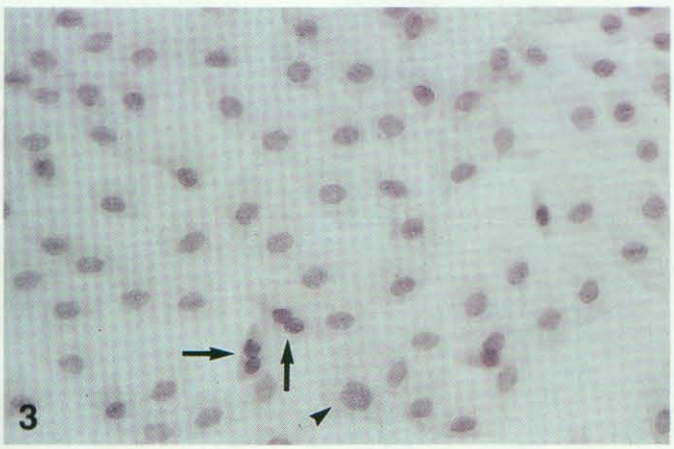
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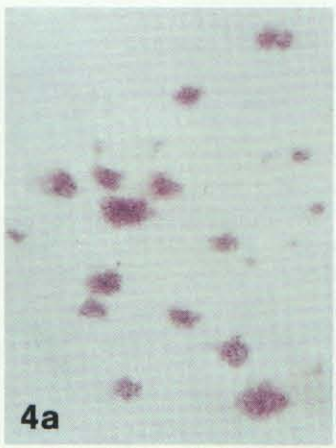
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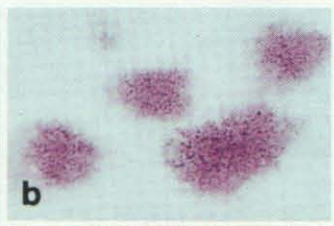
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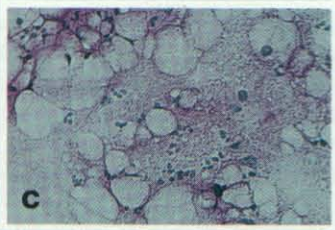
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d


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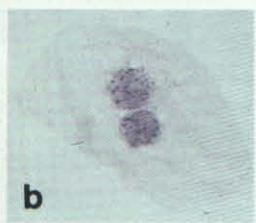
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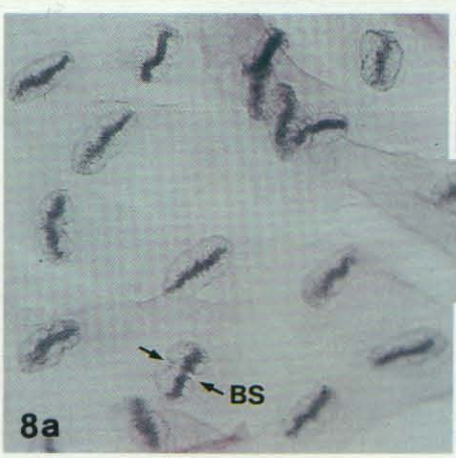
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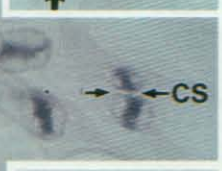
CS


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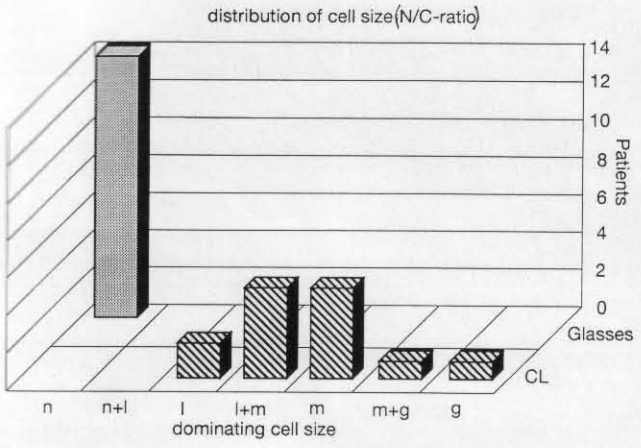

Fig. 9. Significant differences (exact p-value <0.0001) in cell size at upper bulbar conjunctiva between patients wearing glasses and contact lenses (*CL*). *n*, normal-sized cells; *l*, little, enlarged cells; *m*, medium enlarged cells; *g*, large cells

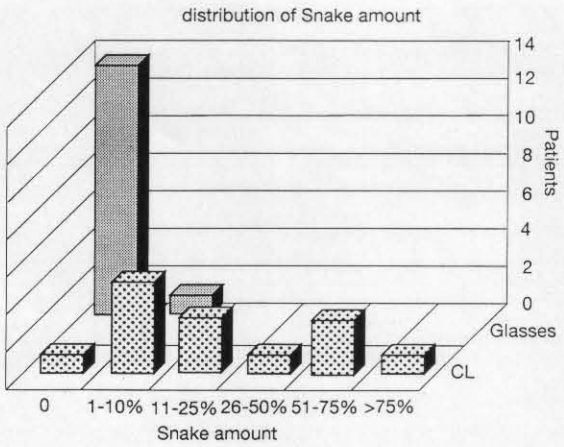

Fig. 10. Occurrence and amount of nuclear chromatin condensations (snakes) at upper bulbar conjunctiva showing significant differences (exact p-value <0.0001) in wearers of glasses and contact lens wearers (*CL*)

tions of nuclear material (Fig. 8c, arrow). Occasionally large nuclei (Fig. 3) occurred, which led to anisonucleosis. Sometimes there were two or more nuclei in one cell (Fig. 3, 5b, 6b); preferably larger cells ('g' and 'xg') showed this phenomenon. Very large squamous cells ('xg') regularly expressed pyknosis (Fig. 5b), which might be followed by fragmentation of the nucleus (Fig. 6a, arrow).

The most interesting and frequent nuclear alteration was the presence of a condensation of nuclear chromatin into an elongated snakelike structure [15, 17], which happened inside an intact nuclear envelope, as seen by light microscopy (Fig. 8a). Various intermediate stages of chromatin condensation were observed. The nucleoli were no longer recognizable in these nuclei by LM. Sometimes these cells showed a kind of segmentation of the elongated nucleus by invagination of the nuclear envelope, and the condensation was preserved, but divided in this process (Fig. 8a, BS and CS).

In our patients snakes have preferably been observed in moderately enlarged cells and even in epithelial cells of normal size (Fig. 7), but rarely in highly enlarged cells. They were typically not singly disseminated in the specimens, but arranged in groups or clusters.

Of the year-long contact lens wearers 13 of 14 showed snakes; (compared with one of the controls), in a mean quantity of about 25% (grade II) of the conjunctival cells belonging to the upper bulbar conjunctiva (Table 1). Only one CL wearer was free of snakes, while about one-third had snakes in more than 50% of their cells (Fig. 10), which means that the majority of their cells showed this distinct nuclear abnormality (Fig. 7). These findings were significantly different in both groups (exact p-value <0.0001).

All observed cytological alterations were not evenly expressed in the different regions of the ocular surface, but showed a characteristic topographical orientation (Fig. 11c). On the bulbar conjunctiva only a circular area around the corneal limbus was involved. This zone was wider in the vertical direction (i.e., in the the 6:00 to 12:00 o'clock direction) and narrower in the horizontal direction. Within this area the extent of the cytological abnormality regularly decreased with increasing distance from the limbus, so that even in eyes with major changes normal conjunctival epithelium could be found in the bulbar periphery, for example, near the conjunctival fornix.

In addition, the degree of alteration varied (in areas of the same limbal distance), dependent on the direction (i.e., upward around 12:00 more than down at 6:00 o'clock). This was most obvious in the different amounts of snakelike condensations found.

The maximum amount clearly occurred in the upper bulbar conjunctiva at around 12:00 o'clock with a mean snake amount of about 25% of the obtained cells. In the lower bulbar area at 6:00 o'clock, the amount was reduced to about 10% (grade I). At the sides of the bulbus (3:00 and 9:00) the occurrence of snakes was even more reduced.

Goblet cells. In all patients GCs showed a normal morphology. Their density revealed by IC at the upper bulbar conjunctiva showed a number of 134 GC/mm^2 (standard deviation 95 GC/mm^2). This is a GCD, which is low compared with histological [13] and other IC evaluations [25, 26]. The average GCD in the controls was 170 ($\pm$56), which is relatively low as well.

The evaluation of GC density proved to be difficult with the method of impression cytology (see also [27], 'comments and responses'), and repeated counts in some patients revealed even higher standard deviations than the reported ones. In contrast to real histological evaluations of conjunctival GCD, as performed very accurately by Kessing [12, 13], the IC technique usually only rendered imprints of mucus coming out of GCs (Fig. 4a, b) instead of the whole GC itself (Fig. 2a, b). Only exceptionally was it possible to detect whole GCs if there were areas on the filter that had a thickness of more than one cell layer. These were not sufficient for quantification. Although originating from single GCs, evalua-

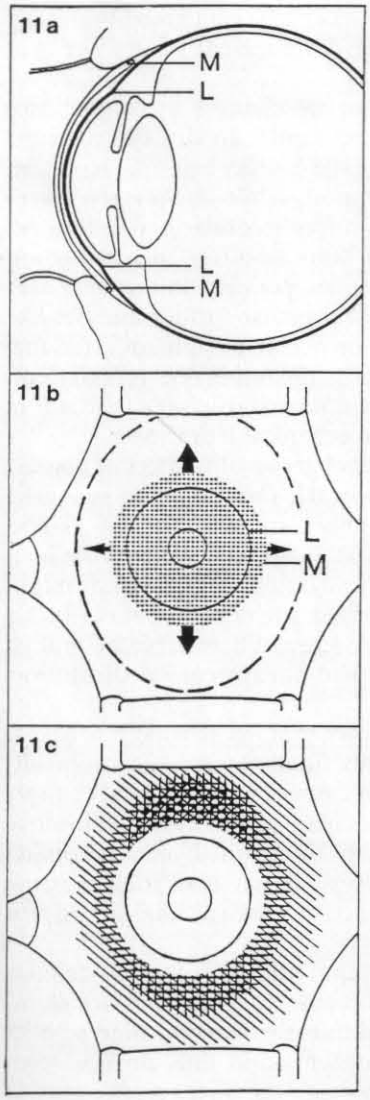

Fig. 11a–c. Topography of ocular surface in relation with contact lens localization and cytological changes. **a** Margin (*M*) of contact lens lies on the conjunctival epithelium in a zone a few millimeter from the limbus (*L*); **b** *Big arrows* indicate the preferred axis of contact lens movement on the eye (i.e., vertical direction); **c** Topographical distribution of cytological changes in the bulbar epithelium (increased degree of *hatching* indicates increasing cell alterations). They lie inside the contact lens excursion zone around the limbus and generally decrease from the limbus towards the bulbar periphery. Most of the alterations were at 12 o'clock, with less at 6 and still fewer at the sides (3 and 9). The circular zone directly around the limbus (*white* in the drawing) has not been examined

tion of mere mucus imprints, on the other hand, showed the risk of too many mistakes for exact quantification and therefore resulted in high standard deviations, as seen in both this study and in other studies [25].

Discussion

Year-long asymptomatic wearers of soft contact lenses were examined and found to show remarkable and significant cytological changes in the conjunctival epithelium.

All patients displayed squamous metaplasia, i.e. distinctly enlarged, flattened cells (at least as squamous patches), in a region that normally has a stratified columnar epithelium [31]. Additionally, they had developed frequent nuclear abnormalities, mainly numerous snake-like condensations of nuclear chromatin (snakes).

These are findings that had so far seemed to be restricted to diseases of the ocular surface mostly associated with dry eye syndrome [2, 18, 23, 25, 27, 28, 32, 36]. In particular, the appearance of squamous metaplasia was only known in ocular disease states, while snakes, first detected in patients with KCS [24], were seen in some contact lens wearers [8]. Unlike the above-mentioned ocular disease states, which additionally develop epithelial keratinization, our patients did not showed this.

The findings of mucus in foamy heaps and strands both with entrapped cells and debris (Figs. 4c, d) showed no significant difference between CL wearers and controls. The mucus strands look similar to those reported by others [3, 10, 12] since they also interconnect GC sites in a net-like manner and may share the supposed involvement in the cleaning system of the ocular surface [3]. In the present study IC appeared to be no ideal method for exact GC counts since it usually only collected mucus imprints of GCs, rarely GCs itself. Counts could be falsely low if not even imprints are obtained, falsely high if one GC produced more than one imprint, or not clearly detectable (smeared) ones. In addition, the investigated region near the limbus and frequently used by IC investigators is no ideal place for comparative GC counts since it shows rapidly increasing GCD towards the fornix, varying about 100% from 3–5 mm limbal distance [12].

The fact that snakes were predominantly found in cells or minor enlargement and even occurred in those of normal size (although they were generally seen in cells of all sizes) suggests that they might be the product of a vital cell reaction in compensation for a stress (factor), which in this case necessarily seems to be represented by the contact lens. The observation of various intermediate stages indicates a process of probably a progressive nature [17]. On the other hand, nuclear chromatin condensations are usually a sign of decreased metabolic activity, and snakes would then represent the final stages of cellular dysregulation.

In the present study it was possible for the first time to demonstrate snakes in localizations other than the upper bulbar conjunctiva. This was successful in all patients (six) with snakes, who were investigated beyond 12:00 o'clock. Hence snakes do not seem to be confined to this area where they were discovered and where they have been expected so far [24, 26, 28] comments and responses.

In asymptomatic contact lens wearers these remarkable alterations are a surprising finding. All of the changes observed in the conjunctival epithelium are caused by contact lens wear. This was the only difference between these patients and the control group and after omission of contact lenses (in two patients for about 2 years), the epithelial changes proved to be reversible.

Furthermore, the topographic distribution of cellular alterations following the contact lens excursion zone on the eye (Fig. 11a, b) strongly supports this suggestion.

These alterations are obviously associated with contact lenses and may have arisen due to various pathomechanisms, e.g., metabolic changes (predominantly anoxia), inflammation (on an immunological or infectious basis), or chronic mechanical irritation. The possible influence of low tear flow on epithelial cytology was excluded by Schirmer's test, which showed good results in all contact lens wearers. Anoxia seems insufficient to explain the reduced changes in the lower as opposed to the upper bulbar site and does not seem to be involved in other ocular diseases showing squamous metaplasia. Inflammation, on the other hand, was excluded by slit lamp examination, absence of symptoms, and absence of leucocytes in IC (except in one control with a few granulocytes). Only the hypothesis of chronic mechanical irritation seems to be satisfactory, because it allows all findings to be explained and might well be involved in the pathogenesis of squamous metaplasia in other ocular surface diseases (as shown below).

The concentrated expression of cellular changes in the upper bulbar conjunctiva, already reduced at 6:00 o'clock and further decreasing at the sides indicates their direct mechanical etiology. The most important changes were in direction of the preferred axis of contact lens movement on the eye (Fig. 11b, vertical arrows), where it moves with every blink (about 10 times/min), and its margin may perform a scraping movement over the ocular surface, especially in the perilimbal conjunctival area. Movements to the sides only occur in extreme horizontal eye movements and are much less frequent. The even more pronounced changes at 12:00 compared with 6:00 (Fig. 11c) can be explained by the movement of the lens which during a blink primarily tends to go in the upward direction, followed by recentering. Additionally, there is the weight of the upper eye lid lying on this region and increasing the mechanical force. Hence the observation that the number of snakes is correlated with the severity of the disease (i.e., epithelial stress), as found in dry eye [24], can be confirmed in CL wearers. Another indication for the involvement of chronic mechanical irritation might be the observation that patients with major epithelial changes often had relatively mobile lenses (3/5 with snake amount $>50\%$ and the one with predominately 'g' cells).

The fact that similar cytological changes, including keratinization, have been found in dry-eye-associated ocular diseases does not necessarily contradict the suggestion of a mechanical etiology. Indeed, it seems to be the case that various diseases of the ocular surface affect its integrity and alter the superficial epithelial structure which is believed to cause a reduction in tear film stability [1, 2]. Even contact lens wearers who show an increase in tear mucin level [9, 34], accounting for the wetting capacity [11, 21, 22] nevertheless show a reduction in tear film breakup time [34]. Reduced tear film stability results in increased friction, which also represents mechanical irritation. If chronic, this leads to further damage of the conjunctival epithelium (and possible induction of squamous metaplasia), which is a vicious circle and again reduces tear film stability, finally potentially leading to the development of dry eye syndrome.

The etiology of cytological changes in contact lens wearers hence seems to be similar to dry eye patients. The only difference is that the contact lens may represent a direct mechanical irritation, while in Sjörgren's syndrome, for example, this arises secondarily due to a decrease in the amount of tears resulting in a reduction in tear film stability (besides possibly influencing tear film osmolarity [6]). In other ocular surface diseases like Stevens-Johnson disease or ocular pemphigoid, the metaplastic changes seem to be the result of a primary epithelial damage, which then secondarily affects tear film stability with increasing mechanical irritation.

One patient in the control group of wearers of glasses, who were regarded as normal, showed some snakelike condensations, what seems surprising at first glance. However, since various functional disorders of the ocular surface produce similar cytological changes, it might well be that this patient had slight disturbances in his preocular conditions that were not detectable by routine clinical examination, but had already caused slight morphological changes.

The present study shows that, as is widely believed, it is not only an incorrectly fitted contact lens or unsuitable lens material that can cause severe epithelial changes which could then be accompanied by distinct subjective problems. Even a correctly fitted soft hydrogel contact lens with high oxygen transparency and good wearing comfort can cause distinct cytological changes in the ocular surface.

The importance of the above recorded cellular changes is yet unclear because they did not result, at least within the observed average wearing time of 5.25 years, in any major symptoms and thus do not seem to include a strong pathological significance.

Probably the development of functional consequences requires a longer time, and most likely the problem of the increasing sensation of eye dryness, sometimes reported by year-long contact lens wearers, is due to squamous metaplasia of conjunctival epithelium. On the one hand, these metaplastic epithelial changes could probably result in an increased disposition for neoplastic degeneration, as described in squamous metaplasia for other epithelial areas (cervix uteri [30]). However, this seems to be pure theory since no increased incidence of ocular surface neoplasia has been reported over the last few decades. On the other hand, squamous metaplasia does not even necessarily include a further change into keratinized epithelium, and this was not detected in our patients. One can at least be reassured by the potential reversibility of the cytological changes after omission of contact lens wear, as found in two of our patients.

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