Virchows Archiv A Pathol Anat (1992) 421:133–141

Virchows Archiv A
Pathological Anatomy and Histopathology

Changes in cytokeratin expression accompany squamous metaplasia of the human respiratory epithelium

P. Stosiek[1], M. Kasper[1], and R. Moll[2]

[1] Institut für Pathologie, Klinikum Görlitz GmbH, Girbigsdorfer Strasse 1–3, O-8900 Görlitz, Federal Republic of Germany
[2] Institut für Pathologie, Universität Mainz, Langenbeckstrasse 1, W-6500 Mainz, Federal Republic of Germany

Received December 13, 1991 / Received after revision March 31, 1992 / Accepted April 2, 1992

Summary. To determine the characteristics of metaplastic changes of the nasal respiratory epithelium, the distribution of individual cytokeratins (CKs) was studied immunohistochemically and by two-dimensional gel electrophoresis. The authors define four types of changes of the normal pseudostratified columnar epithelium: (1) transitional pseudostratified epithelium (first unusual CK.: no. 13); (2) stratified columnar epithelium (increased expression of CKs 4 and 13; CKs 7, 8, 18 and 19 reduced); (3) stratified squamous epithelium, nonkeratinized (appearance of CK 16); and (4) stratified squamous epithelium, keratinized (expression of CKs 1 and 10, variable CK5 and 14 patterns in basal cells). These phenotypes were found simultaneously within single specimens, resulting in apparent overall variability in the immunohistochemical staining patterns. Spatially, changes in CK expression towards "normal" parts were not abrupt but rather gradual. Biochemical data confirmed the immunohistochemical findings and added CK 6 to the pattern of altered nasal mucosa. The findings of this study suggest a stem cell metaplasia in the nasal epithelium which is based on its inherent bimodal developmental programme. A gradual loss of normal respiratory epithelial differentiation, as seen by the loss of CKs 7, 8, and 18, was paralleled by the appearance of squamous epithelial type CKs, e.g. the expression of CKs 1, 10 and 13. Basal cell types CKs 5, 14, 17 and 19 were maintained during this process. Implications of these results for general concepts of CK expression in the metaplastic process are discussed.

Key words: Respiratory epithelium – Nasal mucosa – Metaplasia – Stem cell – Cytokeratin

Correspondence to: P. Stosiek, Institut für Pathologie, Klinikum Cottbus, O-7500 Cottbus, Federal Republic of Germany

Introduction

The term metaplasia (μεταπλασισ) coined by Rudolf Virchow (1871) means local transformation or metamorphosis of a regularly occurring tissue type. Three principal types of metaplasia are commonly distinguished: (1) direct metaplasia, i.e. transformation of a differentiated cell into another state of differentiation; (2) indirect metaplasia, which represents the development of alternatively differentiated cells via newly formed indifferent cells; and (3) stem cell metaplasia developing via preexisting pluripotent stem cell. For a recent review, see Leube and Rustad (1991).

Metaplasia has importance not only from the theoretical point of view, but also for practical reasons, since in general, metaplasia means a deviation from the normal differentiation pathway which may have pre-neoplastic significance.

Intermediate filament (IF) distribution pattern in cells and tissues reflects their differentiation or functional specialization state, their histogenesis and their malignant transformation (Franke et al. 1981; Osborn and Weber 1983; Lane and Alexander 1990). In addition to the 20 "typical" epithelial cytokeratins (CKs) a set of 10 "trichocytic" CKs has been demonstrated in the hair follicles and other epithelia (Heid et al. 1988). The different epithelial CKs are expressed in tissue-specific patterns that generally include particular pairs of one type I and one type II keratin (Moll et al. 1982; Sun et al. 1984; Cooper et al. 1985). Therefore, differentiated epithelial cell types can be distinguished from each other by their selective expression of particular sets of CK polypeptides, reflecting their specialization or pathological alteration (Purkis et al. 1990; Stosiek et al. 1990).

The metaplastic squamous change of respiratory epithelium is still a peculiar problem in histopathology. This type of epithelium lines the largest part of the respiratory system. A great number of carcinomas of the respiratory tract may develop from metaplastic cells (Trump et al. 1978).

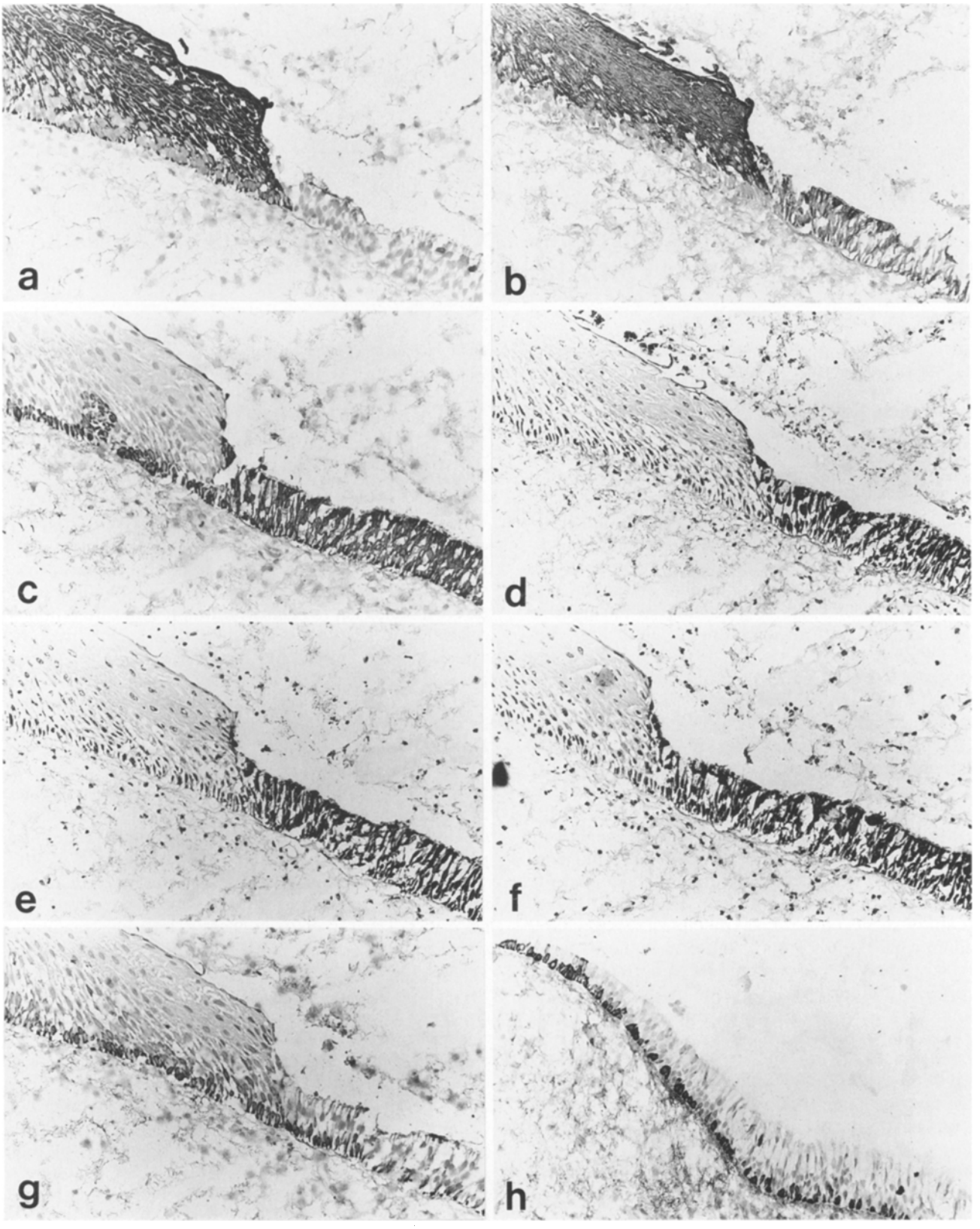

Fig. 1 a–h. "Growth collision" of pseudostratified columnar epithelium (*right*) and stratified, non-keratinized squamous epithelium (*left*). Frozen serial sections immunostained with monoclonal antibodies specific for cytokeratins (CKs) 13 (**a**) and 4 (**b**), 19 (**c**) and 7 (**d**), 8 (**e**), 18 (**f**), and 5 (**g**). **h** Transition of pseudostratified columnar epithelium to transitional (*right*); basal cells are strongly positive with CK 14/17-specific antibody (compare Fig. 3 b). **a–h** Immunoperoxidase, ×490

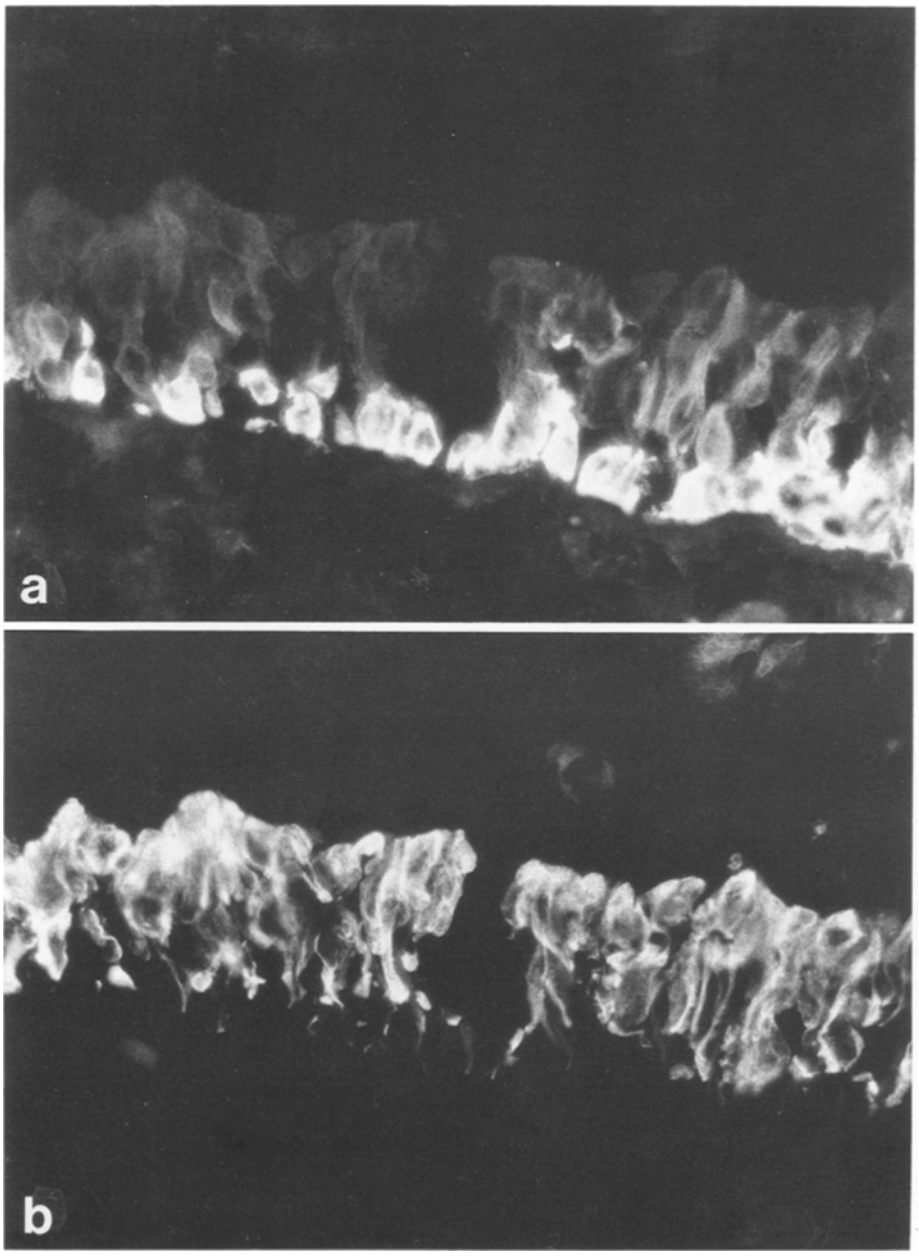

Fig. 2a, b. Double-label immunofluorescence microscopy of pseudostratified columnar epithelium using rabbit antibodies against CK 14 (**a**) and monoclonal antibody LE61 against CK 18. Note that CK 18 expression (**b**) excluded the basal cell layer, which was CK 14 positive (**a**). Immunofluorescence, ×280

Since the diagnosis of metaplastic changes of epithelia located in the lower part of the airways is complicated because of the relative difficulty of obtaining biopsy specimens, we examined the respiratory nasal mucosa in which, when chronically inflamed, metaplastic changes are frequent and can easily be obtained by biopsy.

Materials and methods

Biopsy specimens (fresh tissues) from the nasal and, in some instances, the paranasal sinus mucosa from 27 patients (aged 8–63 years, no sex bias) with chronic inflammatory polyps were immediately embedded in mounting medium (Jung, Heidelberg, FRG) and snap frozen in liquid nitrogen.

The indirect immunoperoxidase technique was performed on unfixed cryostat sections (4 μm thick; mostly consecutively numbered serial sections; for details, see Kasper et al. 1989a). The following monoclonal mouse antibodies to intermediate filament proteins were used:

1. Broad-range anti-CK antibody A45-B/B3 (Karsten et al. 1983; Kasper et al. 1987)
2. Selective antibodies: AE14 specific for CK 5 (Lynch et al. 1986; kindly supplied by Dr. T.-T. Sun, New York, USA); RCK 105 and LP1K against CK 7 (RCK 105: Ramaekers et al. 1987, a gift from Dr. F.C.S. Ramaekers, Maastricht, The Netherlands); LP1K: (Lane et al. 1985; a gift of Dr. E.B. Lane, Dundee, UK); 1C7 reactive for CK 13, and 6B10 specific for CK 4 (Van Muijen et al. 1986; donated by Dr. G.N.P. van Muijen, Nijmegen, The Netherlands); RKSE60, LH2, and LH3, all specific for CK 10 (Lane et al. 1985; Ramaekers et al. 1985); M 20 specific for CK 8 (Schaafsma et al. 1990); LL001 and LL002 specific for CK 14 (Purkis et al. 1990); DC10 and LE61 reactive for CK 18 (Lane 1982; Lauerova et al. 1988); LL025 specific for CK 16, and LL020 specific for CKs 5 and 6 (unpublished; kind gift from Dr. E.B. Lane); E3 specific for CK 17 (Guelstein et al. 1988); SK2-27

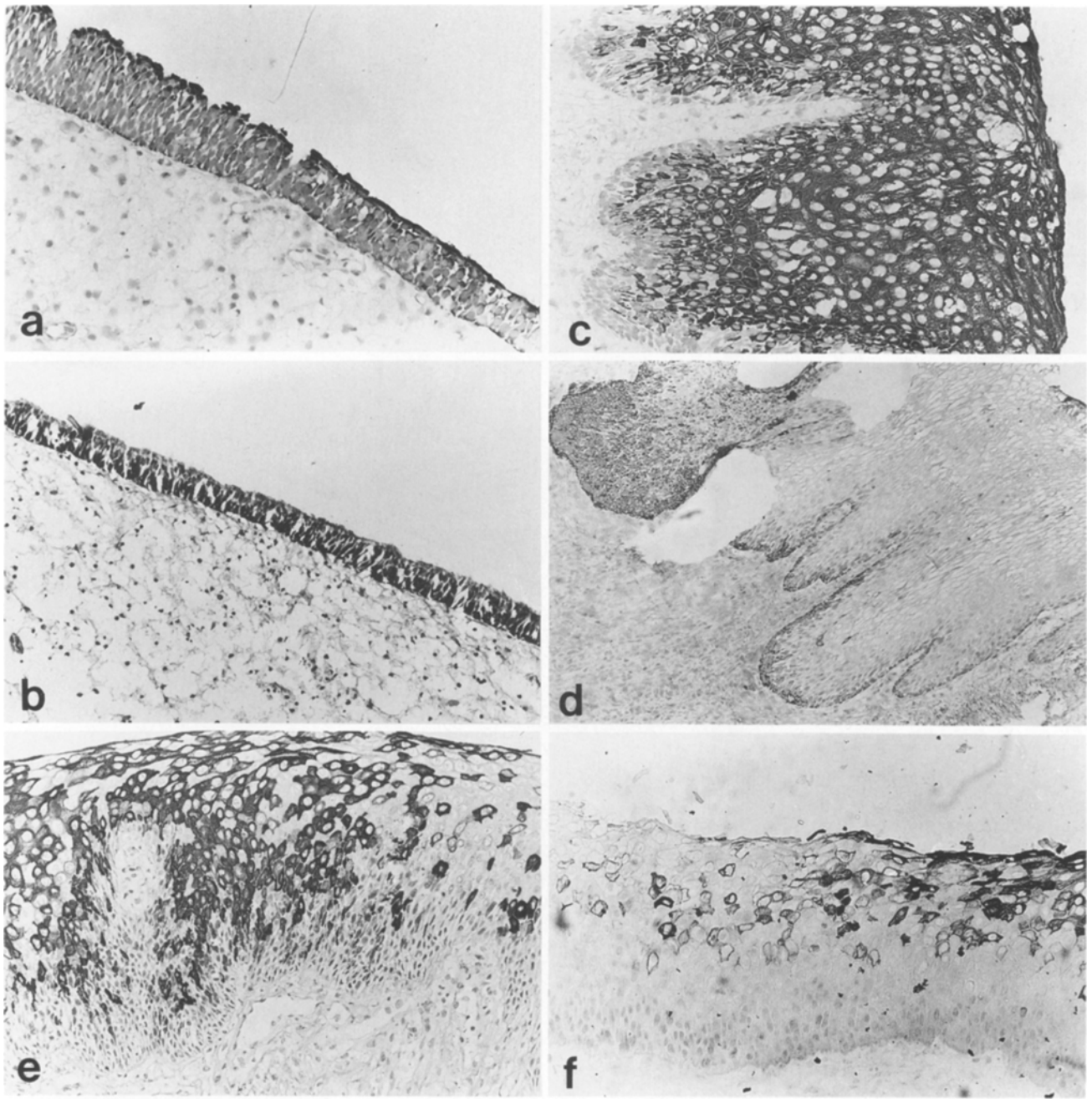

Fig. 3. a–f. Transition of pseudostratified columnar epithelium (*right*) to pseudostratified columnar epithelium, transitional (*left*); more luminal expression of CK 13 on the left. **b** Pseudostratified columnar epithelium with unusual staining for CK 17. **c–f** Stratified squamous epithelium. **c** Suprabasal layers in keratinized areas are strongly positive with CK-13-specific antibody; basal cells are unstained. **d** In parakeratotic areas basal cells lack detectable CK 19 (*right*). **e** In such areas CK 4 was only sparsely expressed in suprabasal cells (*right*). **f** Parakeratotic cells expressed CK 10, ×490

against CKs 14 and 17 (Cintorino et al. 1988) and A53-B/A2 and BA17 against CK 19 (Bartek et al. 1985; Karsten et al. 1985). In all cases, undiluted hybridoma supernatants were used.

3. A monoclonal antibody against vimentin, VIM-3B4 (Progen, Heidelberg, FRG; 1:200 diluted).

Negative controls included omission of the primary antibody and replacement with hybridoma culture medium or phosphate-buffered saline. Human conjunctival epithelium and liver taken from our frozen section bank were used for squamous and simple epithelium type CKs as positive control. For double label immunofluorescence (Kasper 1991) a polyclonal CK 14 antiserum (kind gift from Dr. E.B. Lane), diluted 1:20, and TRITC-labelled anti-rabbit immunoglobulin (Cappel, Cochranville, Pa., USA), diluted 1:40, were used in conjunction with the monoclonal antibodies LP1K, LE61 and M 20 and fluorescence isothiocyanate-conjugated goat anti-mouse immunoglobulin (Cappel), diluted 1:80.

For biochemical analysis of CK polypeptide patterns, the epithelium of interest (e.g. squamous metaplastic foci) was microdissected from 20-µm-thick cryostat sections. After extraction using a high-salt-Triton -X-100 buffer, proteins of the insoluble cytoskeletal residue were separated by two-dimensional gel electrophoresis, using non-equilibrium pH gradient (NEPHG) electrophoresis in the first dimension and SDS polyacrylamide gel electrophoresis (SDS-PAGE) in the second dimension. Proteins were visualized

using a silver staining procedure. These methods have been described previously (Moll et al. 1982; Achtstätter et al. 1986).

Results

Pseudostratified columnar epithelium

In all cases studied, histologically normal-appearing areas of the respiratory epithelium (pseudostratified columnar epithelium) without any pathological changes were detectable. In immunoperoxidase staining, the typical two- to three-layered columnar epithelium exhibited a uniform staining pattern for CKs 7, 8, 18 and 19 (Fig. 1c–f). While immunoreactivity for these CKs was clearly present in the columnar cells, including their foot processes, the small basal cells situated between these processes were negative for CKs 7, 8 and 18, as could be particularly clearly demonstrated using double immunofluorescence (Fig. 2). In contrast, these cells were positive for CK 19 (Fig. 1c). In addition, CKs 5, 14 and 17 were expressed predominantly in basal cells (Figs. 1g, h, 2A). In some cases, an unusual uniform staining pattern has been detected (Fig. 3b). CK 4 could be detected in single basal and in a number of columnar cells. Some columnar cells were, in addition, positive for vimentin (not shown; Kasper and Stosiek 1990).

Pseudostratified columnar epithelium, transitional

In some areas, particularly at the transition zones to the stratified areas, the pseudostratified columnar epithelium exhibited three to four layers of epithelial cells, due to hyperplasia of columnar cells. In general, the same immunohistochemical patterns as described above for the pseudostratified columnar epithelium were found; however, many columnar cells were also immunoreactive for CK13 (Fig. 3a).

Stratified columnar epithelium

The first step in the process of squamous metaplasia was represented by the appearance of stratified columnar epithelium which exhibited morphological signs of true stratification. This was accompanied by prominent changes of the CK pattern. In particular, a strong positivity of mainly suprabasal epithelial cells for CKs 4 and 13 could be seen (Figs. 1a, b, 3c), whereas the expression of CKs 7, 8, 18, and 19 was reduced or even absent (Fig. 1c–g). However, the basal cells showed a CK pattern similar to that of basal cells of the normal pseudostratified columnar epithelium, including prominent expression of CKs 5, 14, and 17 as well as CK 19 (Figs. 1g, 3d).

Stratified squamous epithelium, non-keratinized

These areas are distinguishable from the previously described type of epithelium only by the shape of the suprabasal cells, which exhibited a typical squamous morphology. The CK pattern was quite similar to that of the above-mentioned columnar variant. In addition, a CK16 expression was noted in a subset of suprabasal cells.

Stratified squamous epithelium, keratinized (parakeratosis)

With the onset of keratinization (parakeratosis) a further marked change in the CK composition was observed. The basal cells showed a still prominent CK 17 staining whereas CKs 5 and 14 were only variably detectable. Many suprabasal cells exhibited strong immunostaining for CKs 1 and 10 (Fig. 3f). Interestingly, CKs 4 and 13 disappeared partially, mainly in the parakeratotic areas (Fig. 3e). Vimentin was detected in some metaplastic areas of the respiratory mucosa, in addition to CKs, in a scattered pattern (not shown).

Two-dimensional gel electrophoresis of cytoskeletal proteins of microdissected stratified columnar epithelium revealed the presence of CKs 5, 6, 13, 14, 17, and 19 in high, and CKs 7, 8, and 15 in low proportion (Fig. 4a). Gels of metaplastic non-keratinizing stratified squamous epithelium disclosed the presence of CKs 5, 6, 13, 14, and 17 in major amounts, together with small amounts of CK 19 (Fig. 4b). These biochemical data independently confirm the immunohistochemical results and demonstrate the presence of CK 6, a hyperproliferation-associated component (Weiss et al. 1984), in altered respiratory epithelium.

In general, these phenotypes were often found simultaneously within a given specimen. Thus, the immunohistochemical staining patterns varied considerably throughout the mucosal epithelium. Longitudinal examination along the epithelial lining showed that the changes in CK expression were not abrupt but rather gradual. This suggests that a sequence of morphological and immunohistochemical patterns, as shown schemati-

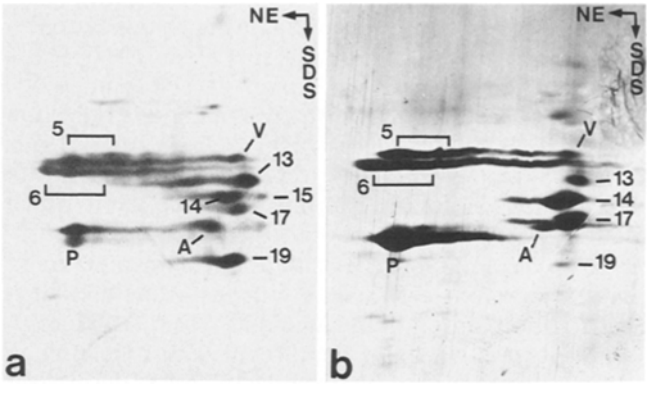

Fig. 4a, b. Two-dimensional gel electrophoresis of cytoskeletal proteins from stratified columnar epithelium (**a**) and metaplastic non-keratinizing stratified squamous epithelium (**b**; from polyp of ethnoid sinus). CKs are denoted by numbers according to Moll et al. (1982). *NE*, Direction of second-dimension SDS-PAGE; *V*, vimentin (mainly from stromal cells); *A*, endogenous actin; *P*, 3-phosphoglycerokinase from yeast added as a marker polypeptide

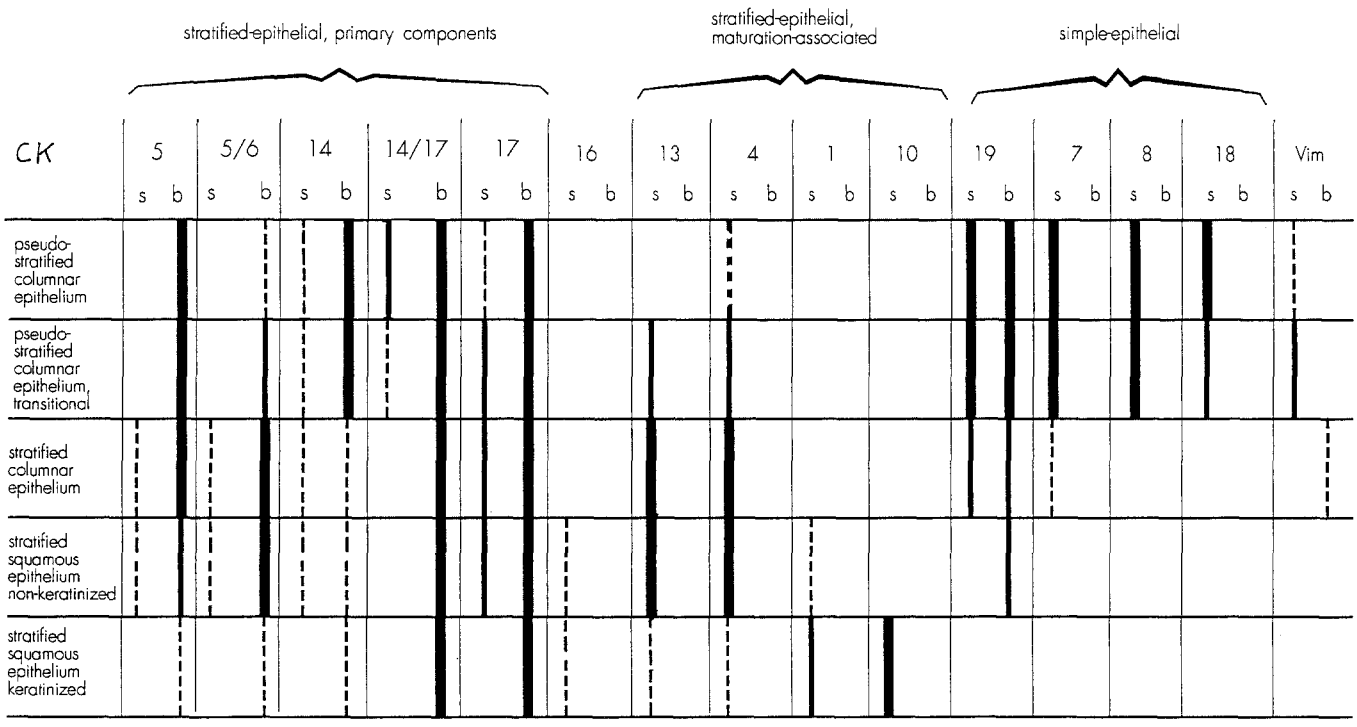

Fig. 5. Schematic representation of the keratin distribution patterns as detected by the different monoclonal antibodies. *Thick line* indicates strong reaction; *thin line* indicates weak reaction; *broken line* indicates inconstant/discontinuous reaction. *s*, suprabasal cells; *b*, basal cells

cally in Fig. 5, is characteristic for the metaplastic process. Abrupt transitions from respiratory to squamous epithelium occurred only rarely and, if so, developed obviously at the borderline between epithelia of extremely different growth rates ("growth collision", Fig. 1 a–g).

Discussion

The respiratory epithelium lining the nasal cavity and paranasal sinuses is of ectodermal origin. Nevertheless, it does not differ morphologically from its endodermally derived prolongation in the bronchial tree (Boenig 1971; Rhodin 1975; Krstic 1984). Metaplastic changes are frequent (Boysen et al. 1986; Carson et al. 1981, 1985; Rossmann et al. 1984; Hosemann and Wigand 1985) and, in general, directed towards squamous epithelium (Zuckerkandl 1892; Hajek 1926; Boysen et al. 1982; Krstic 1984).

The question for the normal cell type from which squamous metaplasia arises is still a matter of controversy. Some authors believe that direct metaplasia of cilia-less secretory cells (small mucous granule cells) is the main mechanism (Wang and Ying 1977; Trump et al. 1978; Boysen et al. 1986; Evans et al. 1986; Sigler et al. 1988). Others consider the metaplastic foci as derivatives of undifferentiated basal cells with bimodal potency (stem cell metaplasia) (Mossmann and Craighead 1975; Reid and Jones 1979; Chopra 1982; Niimi et al. 1987). Finally, both mechanisms or cell types may be responsible for the induction of squamous epithelial metaplasia (Rutten et al. 1988).

The present study firstly reports on the CK composition of ectodermally derived nasal respiratory epithelium. It shows that it is similar to that of endodermally derived bronchial and tracheal respiratory epithelial described previously (Klein-Szanto et al. 1987; for review, see Moll 1987). In addition, CK polypeptides 4 and 14 were found as normal components. Broers et al. (1989) already noted a varying expression of CK4 in columnar cells and of CK14 in basal cells of the respiratory bronchial epithelium. The complex CK pattern of both simple epithelial-type CKs 7, 8, 18 and 19 and stratified-epithelial-type CKs 4, 5, 14, and 17 indicate the bimodality of the respiratory epithelium seen at the tissue level (Moll 1988). At the cellular level, however, these CKs are differentially distributed, the simple-epithelial CKs being expressed predominantly in the columnar cells while the stratified-epithelial CKs prevail in the basal cells. This last fact would support the notion that squamous metaplasia indeed originates from basal cells and is also in line with the experience that the metaplastic potential of the respiratory epithelium is essentially restricted to the squamous type, in contrast to the broader metaplastic potency of the urothelium (Moll 1988; Goertchen et al. 1990) and the gastrointestinal character of the metaplasias observed in the corpus mucosa of the stomach (Stosiek and Kasper 1990). One should note, however, that the CK phenotype of respiratory basal cells is not purely of the squamous type but also includes CK 19, which is a main component of many simple epithelia (Moll et al. 1982), and of respiratory columnar cells. Using certain antibodies, evidence for a limited expression also of CKs 8 and 18 has been

presented for the bronchial epithelium (Broers et al. 1989; Leube and Rustad 1991). Therefore, the CK expression would also be in line with the bimodal potency of the basal cells and with their proposed stem cell character, i.e. their ability to give rise to simple epithelial columnar cells (Inayama et al. 1988; for a different model of respiratory epithelial regeneration, see, for example, Sigler et al. 1988). In the present study, we could distinguish, both morphologically and in terms of CK expression, several epithelial entities which we interpret as sequential temporal steps towards squamous metaplasia.

The earliest recognizable differentiation change appears to have taken place in areas which we have designated the "respiratory transitional zone" and which seemingly have not yet been described as a morphological entity. In these areas, the pseudostratified morphology is still maintained but the epithelium is slightly thickened due to columnar cell hyperplasia. Morphologically, the respiratory transitional zone is comparable with the first metaplastic changes described by Sigler et al. (1988) in serum-free organ explantation cultures of tracheal epithelium. The changes in CK expression are only minor. Since the basal cells maintain their typical CK set and the basic structure of the epithelium remains unchanged, we consider this epithelial lesion as reparative and reversible and as the initial stage of squamous metaplasia originating in basal cells. The subsequent two steps, however, are characterized by profound changes both in morphology, including loss of cilia (Carson et al. 1981) and development of true stratification (i.e. loss of basal membrane contact of suprabasal cells), and in terms of CK expression. A stepwise loss of simple epithelial-type CKs and neo-expression of CKs which are typical of stratified squamous differentiation has already be found at other sites. Examples are the expression of CKs 4 and 13 in the non-cornifying stratified squamous epithelium at the upper digestive tract, or of CKs 1 and 10 in the cornifying epithelium of the epidermis (for references, see Moll 1987; Morgan et al. 1987).

Throughout all stages of metaplasia, the basal cells more or less maintain their characteristic CK pattern (CKs 5, 14, 17, 19). This means that the putative stem cells themselves are essentially excluded from the changes of the remaining epithelium although minor changes may occur, such as focal reduction of staining for CK 5 (for reduction of CK 17 in some foci of squamous metaplasia of the bronchial mucosa see Leube and Rustad 1991). The relatively high degree of concordance in CK expression between respiratory basal cells and squamous metaplastic basal cells furhter supports the stem cell nature of the respiratory basal cells and the origin of squamous metaplasia from these cells. The lack of maturation-associated CKs in basal cells underlines their low degree of differentiation. All these observations support the concept of stem cell metaplasia originating from basal cells. Similarly, for the tracheobronchial epithelium, the basal cell origin of squamous metaplasia has been suggested by several authors (Niimi et al. 1987; Rutten et al. 1988; Fukuda et al. 1989).

The analysis of CK expression allows deeper insights into the actual cell differentiation as compared to the conventional histology. Thus, differences in the expression of certain CK polypeptides between metaplastic stratified squamous epithelium and neighbouring morphologically identical non-metaplastic stratified squamous epithelium may become obvious (cf. Morgan et al. 1987). Moreover, different metaplastic foci may differ with regard to certain CK components which may be related to differences in the degree of differentiation and maturation (non-keratinized versus keratinized; Fig. 5) but, possibly, also to other tpyes of changes. For example, in a recent study on bronchial squamous metaplasia, a tendency for increased expression of simple-epithelial CKs (in additional to those of stratified epithelium-type) in metaplastic foci with dysplastic changes was noted (Leube and Rustad 1991; Moll 1992). Related tendencies have been described to occur during dysplastic changes of the stratified squamous epithelium of the cervix uteri which is often of metaplastic origin (Smedts et al. 1990), and during premalignant changes of the oral mucosa (Lindberg and Rheinwald 1989).

Squamous metaplasia of the respiratory mucosa is considered as an important step in the development of squamous cell carcinomas (WHO 1978; Boysen and Reith 1983). It remains to be determined in further studies whether the analysis of individual CK patterns may be of diagnostic value in determining the malignant potential of metaplastic lesions.

Acknowledgement. This work was supported by grants from the Fritz-Thyssen-Stiftung.

References

Achtstätter T, Hatzfeld M, Quinlan RA, Parmelee DC, Franke WW (1986) Separation of cytokeratin polypeptides by gel electrophoretic and chromatographic techniques and their identification by immunoblotting. Methods Enzymol 134:355–371

Bartek J, Durban EM, Hallowes RC, Taylor-Papadimitriou J (1985) A subclass of luminal cells in the human mammary gland defined by monoclonal antibodies to cytokeratins. J Cell Sci 75:1–17

Boenig H (1971) Leitfaden der Entwicklungsgeschichte des Menschen. Thieme, Leipzig, p 159

Boysen M (1985) Histopathology of the nasal mucosa in furniture workers. Rhinology 23:109–111

Boysen M, Reith A (1983) Discrimination of various epithelia by simple morphometric evaluation of the basal cell layer. Virchows Arch [B] 42:173–184

Boysen M, Morton PF, Pilström L, Solberg LA, Torp T (1982) A simple and efficient method for objective discrimination between pseudostratified, metaplastic and dysplastic nasal epithelium. J Microsc 130:99–106

Boysen M, Voss R, Solberg LA (1986) The nasal mucosa in softwood exposed furniture workers. Acta Otolaryngol (Stockh) 101:501–50

Broers JL, Leij L, Klein-Rot M, Haar A, Lane EB, Leigh IM, Wafenaar SS, Vooijs GP, Ramaekers FCS (1989) Expression of intermediate filament proteins in fetal and adult human lung tissues. Differentiation 40:119–128

Carson JL, Collier AM, Knowles MR, Boucher RC, Rose JG (1981) Morphometric aspects of ciliary distribution and ciliogenesis in human nasal epithelium. Proc Natl Acad Sci USA 78:6996–6999

Carson JL, Collier AM, Hu SS (1985) Aquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N Engl J Med 312:463–46

Chopra DP (1982) Squamous metaplasia in organ cultures of vitamin A-deficient hamster trachea: cytokinetic and ultrastructural alteration. J Natl Cancer Inst 69:895–905

Cintorino MTDVM, Bugnoli M, Petracca R, Leoncini P (1988) Cytokeratin pattern in normal and pathological bladder urothelium: immunohistochemical investigation using monoclonal antibodies. J Urol 139:428–432

Cooper D, Schermer A, Sun T-T (1985) Classification of human epithelia and their neoplasms using monoclonal antibodies to keratins: strategies, applications, and limitations. Lab Invest 52:243–256

Evans MJ, Shami SG, Cabral-Anderson LJ, Dekker NP (1986) Role of nonciliated cell in renewal of the bronchial epithelium of rats exposed to NO_2. Am J Pathol 123:126–133

Franke WW, Schiller DL, Moll R, Winter S, Schmidt E, Engelbrecht J, Denk H, Krepler R, Platzer B (1981) Diversity of cytokeratins. Differentiation specific expression of cytokeratin polypeptides in epithelial cells and tissues. J Mol Biol 153:933–959

Fukuda Y, Takemura T, Ferrans VJ (1989) Evolution of metaplastic squamous cells of alveolar walls in pulmonary fibrosis produced by paraquat. An ultrastructural and immunohistochemical study. Virchows Arch [B] 58:27–43

Goertchen R, Kasper M, Stosiek P (1990) Das mucourotheliale Karzinom der Harnblase. Pathologe 11:166–170

Guelstein VI, Tchypysheva TA, Ermilova VD, Litvinova LV, Troyanovsky SM (1988) Monoclonal antibody mapping of keratins 8 and 17 and of vimentin in normal human mammary gland, benign tumors, dysplasias and breast cancer. Int J Cancer 42:147–253

Hajek M (1926) Pathologie und Therapie der entzündlichen Erkrankungen der Nebenhöhlen der Nase. Deuticke, Leipzig, p 98

Heid HW, Moll I, Franke WW (1988) Patterns of expression of trichocytic and epithelial cytokeratins in mammalian tissues. I. Human and bovine hair follicles. Differentiation 37:137–157

Hosemann W, Wigand ME (1985) Örtliche Unterschiede im Gewebebild der chronisch-hyperplastischen Nasennebenhöhlenschleimhaut. Pathology 33:311–315

Inayama Y, Hook GER, Brody AR, Cameron GS, Jetten AM, Gilmore LB, Gray T, Nettesheim P (1988) The differentiation potential of tracheal basal cells. Lab Invest 58:706–777

Karsten U, Widmaier R, Kunde D (1983) Monoclonal antibodies against antigens of the human mammary carcinoma cell line MCF-7. Arch Geschwulstforsch 53:529–536

Karsten U, Papsdorf G, Roloff G, Stolley P, Abel H, Walther I, Weiss H (1985) Monoclonal anti-cytokeratin antibody from a hybridoma clone generated by electrofusion. Eur J Cancer Clin Oncol 21:733–740

Kasper M (1991) Heterogeneity in the immunolocalization of cytokeratin specific monoclonal antibodies in the rat eye: evaluation of unusual epithelial tissue entities. Histochemistry 95:613–620

Kasper M, Stosiek P (1990) The expression of vimentin in epithelial cells from human nasal mucosa. Eur Arch Otorhinolaryngol 248:53–56

Kasper M, Stosiek P, Typlt H, Karsten U (1987) Histological evaluation of three new monoclonal anti cytokeratin antibodies. 1. Normal tissues. Eur J Cancer Clin Oncol 23:137–147

Klein-Szanto AJP, Boysen M, Reith A (1987) Keratin and involucrin in preneoplastic and neoplastic lesions. Arch Pathol Lab Med 111:1057–1061

Krstic RV (1984) Illustrated encyclopaedia of human histology. Springer, Berlin Heidelberg New York, p 348

Lane (1982) Monoclonal antibodies provide specific intramolecular markers for the study of epithelial tonofilament organization. J Cell Biol 92:665–673

Lane EB, Alexander CM (1990) Use of keratin antibodies in tumor diagnosis. Cancer Biol 1:165–169

Lane EB, Bartek J, Purkis PE, Leigh IM (1985) Keratin antigens in differentiating skin. Ann NY Acad Sci 455:241–258

Lauerova L, Kovarik J, Bartek J, Rejthar A, Vojtesek B (1988) Novel monoclonal antibodies defined epitope of human cytokeratin 18 molecule. Hybridoma 7:495–504

Leube RE, Rustad TJ (1991) Squamous cell metaplasia in the human lung: molecular characteristics of epithelial stratification. Virchows Arch [B] 61:227–253

Lindberg K, Rheinwald JG (1989) Suprabasal 40 kd keratin (K19) expression as an immunohistologic marker of premalignancy in oral epithelium. Am J Pathol 134:89–98

Lynch MH, O,Guin WM, Hardy C, Mak L, Sun T-T (1986) Acidic and basic hair/nail ("hard") keratins. Their co-localization in upper cortical and cuticle cells of human hair follicle and their relationship to "soft" keratins. J Cell Biol 103:2593–2606

Moll R (1987) Epithelial tumor markers: cytokeratins and tissue polypeptide antigen. In: Seifert G (ed) Morphological tumor markers. Springer, Berlin Heidelberg New York, pp 71–102

Moll R (1988) Differenzierungsprogramme des Epithels und ihre Änderungen. Verh Dtsch Ges Pathol 72:102–114

Moll R (1992) Cytokeratine als Differenzierungsmarker: Expressionsprofile von Epithelien und epithelialen Tumoren. In: Seifert G (ed) Veröffentlichungen aus der Pathologie. Fischer, Stuttgart (in press)

Moll R, Franke WW, Schiller DL, Geiger B, Krepler R (1982) The catalogue of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 31:11–24

Moll R, Schiller D, Franke WW (1990) Identification of protein IT of the intestinal cytoskeleton as a novel type I cytokeratin with unusual properties and expression patterns. J Cell Biol 111:567–580

Morgan PR, Leigh JM, Purkis PE, Gardner JD, Muijen GNP van, Lane EB (1987) Site variation in keratin expression in human oral epithelia. Epithelia 13:31–43

Mossmann BT, Craighead JE (1975) Long-term maintenance of differentiated respiratory epithelium in organ culture. Proc Soc Exp Biol Med 149:227–233

Niimi T, Imaizumi M, Abe T, Haimoto H, Nagura H (1987) Immunohistochemical characteristics of proliferative and metaplastic lesions in bronchial mucosa. Am J Clin Pathol 8 8:545–551

Osborn M, Weber K (1983) Tumor diagnosis by intermediate filament typing: a novel tool for surgical pathology. Lab Invest 48:372–388

Purkis PE, Steel JB, Mackenzie IC, Nathrath WBJ, Leigh IM, Lane EB (1990) Antibody markers of basal cells in complex epithelia. J Cell Sci 97:39–50

Ramaekers FCS, Moesker O, Huysmans A, Schaat G, Westerhof G, Wagenaar SS, Herman CJ, Vooijs GP (1985) Intermediate filament proteins in the study of tumor heterogeneity: an in-depth study of tumors of the urinary and respiratory tracts. Ann NY Acad Sci 455:614–634

Ramaeckers FCS, Huysmans A, Schaart G, Mosker O, Vooijs P (1987) Tissue distribution of keratin 7 as monitored by a monoclonal antibody. Exp Cell Res 170:235–249

Reid C, Jones R (1979) Bronchial mucosal cells. Fed Proc 38:191–196

Rhodin JA (1975) Atlas of histology. Oxford University Press, New York, p 352

Rossmann CM, Lee RM, Forrest JB, Newhouse MT (1984) Nasal ciliary ultrastructure and function in patients with primary ciliary dyskinesia compared with that in normal subjects and in subjects with various respiratory diseases. Am Rev Respir Dis 129:161–167

Rutten AA, Bruyntjes JP, Ramaekers FCS (1988) Effect of cigarette smoke condensate and vimentin A depletion in keratin expression patterns in cultured hamster tracheal epithelium. Virchows Arch [B] 56:111–117

Schaafsma HE, Ramaekers FCS, Muijen GNP van, Lane EB, Leigh IM, Robben H, Huijsmans A, Ooms ECM, Ruiter DJ (1990) Distribution of cytokeratin polypeptides in human transitional cell carcinomas, with special emphasis on changing expression patterns during tumor progression. Am J Pathol 136:329–343

Sigler RE, Newkirk C, McDowell EM (1988) Histogenesis and morphogenesis of epidermoid metaplasioa in hamster tracheal organ explant culture. Virchows Arch [B] 55:47–55

Smedts F, Ramaekers FCS, Robben H, Pruszcynski M, Muijen GNP van, Lane EB, Leigh I, Vooijs P (1990) Changing patterns of keratin expression during progression of cervical intraepithelial neoplasia. Am J Pathol 136:657–668

Stosiek P, Kasper M (1990) Neoexpression von Cytokeratin 7 bei der chronisch-atrophischen Gastritis mit perniziöser Anämie. Pathologe 11:14–17

Stosiek P, Kasper M, Karsten U (1990) Expression of cytokeratins 8 and 18 in human Sertoli cells of immature and atrophic seminiferous tubule. Differentiation 43:66–70

Sun T-T, Eichner R, Schermer A, Cooper D, Nelson WG, Weiss RA (1984) Classification, expression and possible mechanisms of evaluation of mammalian epithelial keratins: an unifying model. In: Sun (ed.) The transformed phenotype, cancer cell, vol 1. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, pp 169–176

Trump BF, McDowell EM, Glavin F, Barett LA, Becci PJ, Schüsel W (1978) The respiratory epithelium. III. Histogenesis of epidermoid metaplasia and carcinoma in situ in the human. J Natl Cancer Inst 61:563–575

Van Muijen GNP, Ruiter DJ, Franke WW, Achtstätter T, Haasnoot WHB, Poneck M, Warnaar SO (1986) Cell type heterogeneity of cytokeratin expression in complex epithelia and carcinomas as demontrated by monoclonal antibodies specific for cytokeratins nos 4 and 13. Exp Cell Res 162:97–113

Virchow R (1871) Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre, 4th edn. Hirschwald, Berlin, pp 364–365

Wang NS, Ying WL (1977) The pattern of goblet cell hyperplasia in human airways. Hum Pathol 8:301–311

Weiss RA, Eichner R, Sun T-T (1984) Monoclonal antibody analysis of keratin expression in epidermal disease: a 48-kD and a 56-kD keratin as molecular markers for hyperproliferative keratinocytes. J Cell Biol 98:1397–1406

WHO (1978) International histological classification of tumors, No. 19. WHO, Geneva

Zuckerkandl E (1892) Normale und pathologische Anatomie der Nasennebenhöhle und ihrer pneumatischen Anhänge. Braunmüller, Vienna, p 77