Virchows Arch. A Path. Anat. and Histol. 384, 109–120 (1979)

Virchows Archiv A

Plasma Cells and Immunoglobulin-Synthesis in Oral Precancer and Cancer

Correlation With Dysplasia, Cancer Differentiation, Radio- and Chemotherapy

Thomas Löning and Arne Burkhardt*

Institute of Pathology, University of Hamburg (Director: Prof. Dr. G. Seifert), Martinistr. 52, D-2000 Hamburg 20, Federal Republic of Germany

Summary. The subepithelial and peritumoral inflammatory infiltrates of 202 oral premalignant and malignant lesions – 108 leukoplakias and 94 squamous cell carcinomata with different grades of dysplasia were examined using an immunoenzymatic method. In addition, the influence of radiation and bleomycin-therapy on the stromal reaction of 24 carcinomata was studied.

The incidence of immunoglobulin labelled plasma cells (IgA and IgG) was twice as high in those cases of leukoplakia where dysplasia was present.

The number of plasma cells, especially IgA- and IgG-containing plasma cells, decreased significantly with progressive tumor dedifferentiation.

The plasma cell response differed before and after radiation with a decrease in IgA- and IgG-containing plasma cells after therapy. In contrast, bleomycin-therapy did not produce distinct changes in the humoral and cellular stromal reaction. In the epithelium, IgA and IgG were localized throughout all epithelial layers in leukoplakias with dysplasia. This finding indicates a leakage of locally synthesized immunoglobulins through an altered oral mucosa.

This investigation reveals alterations in the local immune homoeostasis of the oral mucosa in premalignant and malignant lesions which varies with the grade of dysplasia, tumor differentiation and therapy.

Key words: Plasma cell – Immunoglobulins – Leukoplakia – Squamous cell carcinoma – Tumor therapy.

Introduction

In a recent study 656 cases of oral leukoplakia were analyzed according to their histological-cytological differentiation and the epithelial-mesenchymal in-

* This study was supported by a grant from the Deutsche Forschungsgemeinschaft

Send offprint requests to: Dr. Th. Löning

0340-1227/79/0384/0109/$02.40

terrelation, i.e. the stromal reaction by lymphocytes and plasma cells (Burkhardt and Seifert, 1977). Ten percent of the leukoplakias, clinically defined as a "white patch of the mucosa" (Waldron and Shafer, 1960; Pindborg et al., 1963; Who, 1978) were classified pathologically as precancerous lesions including carcinomata in situ and severe dysplasia. A positive correlation was found between the grade of dysplasia and the density of the stromal lympho-plasma-cellular infiltrate.

In squamous cell carcinomata of the oral cavity the stromal reaction is more pronounced in well differentiated carcinomata with keratinization than in poorly differentiated tumors (Seifert and Burkhardt, 1977).

There is a cellular immune response to the tumor and also a pronounced humoral immune reaction with a local accumulation of immunoglobulin-containing plasma cells (Löning et al., 1977). This, in particular, may influence the growth of tumors and the development of metastases (Ioachim, 1976; Hellström and Hellström, 1976; Lewis et al., 1977).

This paper presents a qualitative-quantitative analysis of the stromal cell response (immunoglobulin-containing cells, lymphocytes, macrophages) in 202 oral leukoplakias and carcinomata in correlation to the grade of dysplasia. In addition we studied the influence of radio- and chemotherapy on the stromal reaction of 24 carcinomata.

Table 1. The stromal cellular pattern and the distribution of immunoglobulin containing plasma cells in oral leukoplakias ($n=108$)

	Leukoplakias					
	without Dysplasia $n=52$		moderate Dysplasia $n=25$		severe Dysplasia $n=31$	
	%	±	%	±	%	±
Stromal cellular pattern (%)*						
plasma cells	38.53	18.23	44.67	17.97	45.84	16.34
lymphocytes	41.44	13.97	39.65	12.98	41.45	13.20
macrophages	6.12	5.05	7.43	4.43	5.52	5.12
granulocytes	5.00	4.73	1.83	1.72	3.19	2.79
Distribution of Ig-containing plasma cells (%)**						
IgA	7.67	5.34	15.44	8.57	14.41	10.82
IgG	13.95	9.48	28.04	14.77	36.62	17.13
IgM	6.00	2.35	7.00	3.07	7.18	5.88

% = mean values; ± = standard deviation; underlined values = $P<0.05$
The percentages are calculated with addition of unclassified mesenchymal cells (*) and unlabelled plasma cells (**)

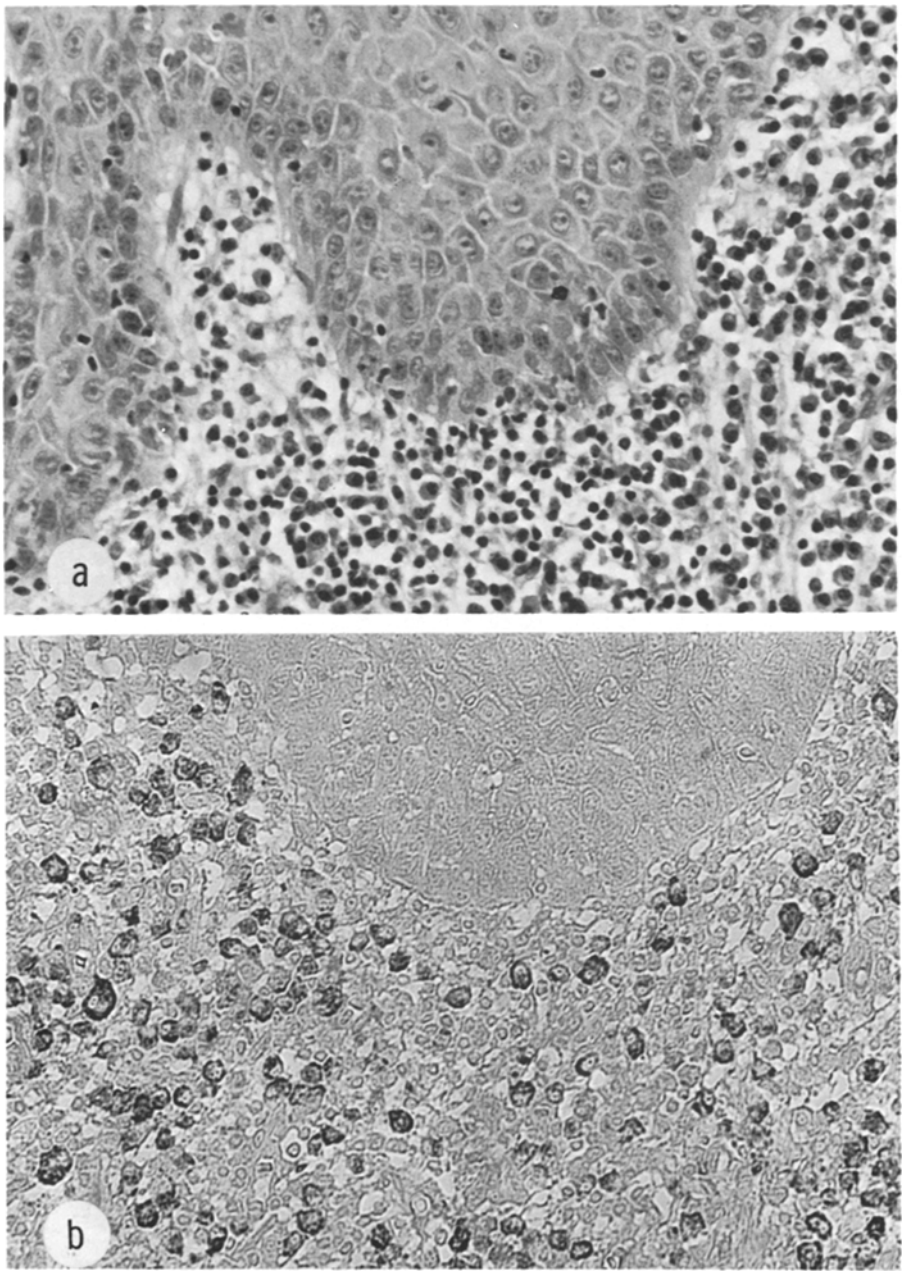

Fig. 1a and b. Leukoplakia with moderate dysplasia. **a** Dense lympho-plasmacellular infiltration around the epithelial rete pegs. HE-stain (× 300). **b** Comparable field from adjacent section. Demonstration of IgG-containing plasma cells (black deposits). Indirect immunoperoxidase technique without counterstaining (× 300)

Table 2. The stromal cellular pattern and the distribution of immunoglobulin containing plasma cells in oral carcinomata ($n=94$)

	Carcinomata (Broder's Grading)							
	Grade I (well diff.) ($n=25$)		Grade II (moderately diff.) $n=21$		Grade III (poorly diff.) $n=28$		Grade IV (undiff.) $n=20$	
	%	±	%	±	%	±	%	±
Stromal cellular pattern (%)								
plasma cells	46.46	14.73	42.75	18.55	31.50	14.19	24.67	17.39
lymphocytes	32.46	12.82	30.25	20.88	41.14	13.97	40.50	11.33
macrophages	9.77	4.38	11.50	4.66	10.68	3.85	13.33	3.56
granulocytes	2.50	2.27	2.00	1.73	5.33	8.78	2.00	1.22
Distribution of Ig-containing plasma cells (%)**								
IgA	41.49	15.02	32.04	14.72	28.45	16.39	22.74	16.59
IgG	44.08	13.77	42.75	20.16	34.72	19.65	22.56	20.84
IgM	14.41	13.45	12.49	10.30	15.38	11.27	11.97	7.58

% = mean values; ± = standard deviation; underlined values = $P<0.05$
The percentages are calculated with addition of unclassified mesenchymal cells (*) and unlabelled plasma cells (**)

Material and Methods

The inflammatory infiltrate was examined in specimens from a group of 202 patients with: leukoplakia without dysplasia (52), leukoplakia with moderate and severe dysplasia (56) and squamous cell carcinomata with different grades of malignancy (94)[1]. In addition, the biopsies of 12 bleomycin-treated and 12 irradiated patients were compared before and after therapy. The grading of the leukoplakias was performed according to Burkhardt and Maerker (1978), and the carcinomata were classified in accordance to the grading of Broders (1920).

Formalin-fixed and paraffin-embedded specimens were cut at 3 µm and then exposed to a range of rabbit antihuman immunoglobulin antibodies and rabbit PAP-complex (for detailed description of the method see: Taylor, 1974, 1978; Löning et al., 1977).

The specifity of the labelling of enzymatic conjugates was controlled by the use of normal rabbit serum instead of specific antisera. Competitive binding was assessed using horse antihuman immunoglobulin.

The slides were examined at a magnification of ×1,000. Four fields per slide were examined and the percentage of lymphocytes, plasma cells, especially immunoglobulin-containing plasma cells, and macrophages were determined. In addition, the epithelial distribution of the different immunoglobulin classes was analyzed.

Results

Sixty percent of the leukoplakias without dysplasia show an inflammatory infiltrate, which consists of 39% plasma cells, 41% lymphocytes and 6% macro-

[1] No cases of leukokeratosis nicotina palati were included in the material

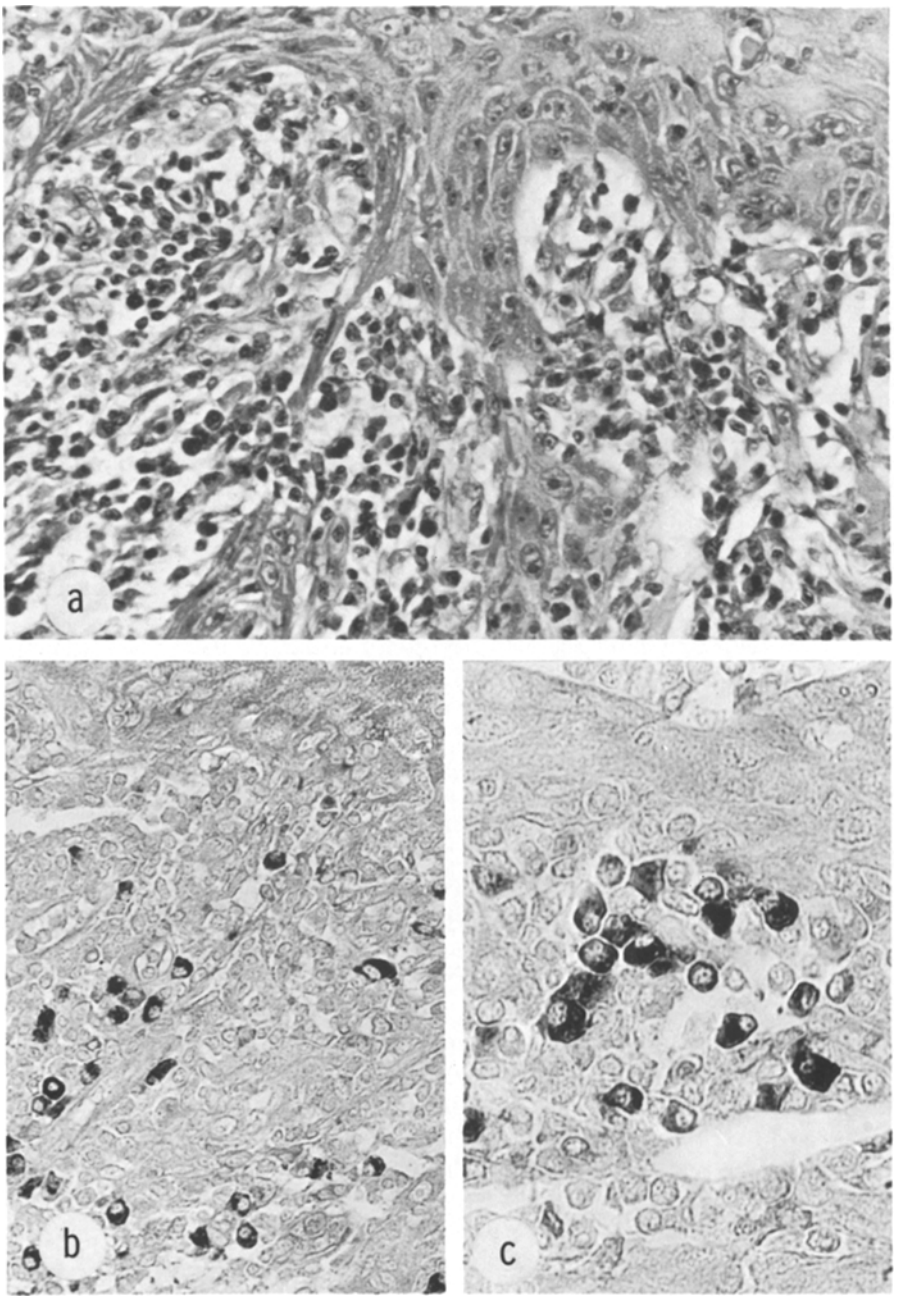

Fig. 2a–c. High differentiated carcinoma. **a** Early tumor invasion accompanied by a marked inflammatory infiltrate. HE-stain (×300). **b** Comparable field from adjacent section. Localization of IgG-containing plasma cells (black deposits) between the tumor cell cords. Indirect immunoperoxidase technique without counterstaining (×300). **c** Higher magnification (×480)

Table 3. The stromal cellular pattern and the distribution of immunoglobulin containing plasma cells before and after radiation or bleomycin-therapy ($n=24$)

	Radiation ($n=12$)				Bleomycin-therapy ($n=12$)			
	before		after		before		after	
	%	±	%	±	%	±	%	±
Stromal cellular pattern (%)*								
plasma cells	50.57	11.43	25.00	12.14	32.60	7.16	51.17	22.60
lymphocytes	29.17	7.28	41.20	10.08	38.80	13.34	29.17	17.59
macrophages	10.43	3.55	11.40	4.28	14.00	4.64	7.83	5.49
granulocytes	1.50	0.84	17.67	16.50	3.00	1.41	2.00	1.41
Distribution of Ig-containing plasma cells (%)**								
IgA	40.12	19.70	21.72	20.87	32.35	6.80	28.55	13.21
IgG	42.63	21.53	23.96	19.42	47.58	20.13	33.24	15.16
IgM	10.24	9.67	13.02	11.82	14.27	6.55	5.40	5.02

% = mean values; ± = standard deviation; underlined values = $P<0.05$
The percentages are calculated with addition of unclassified mesenchymal cells (*) and unlabelled plasma cells (**)

phages (Table 1). Immunoglobulin-containing plasma cells are present in $^2/_3$ of the cases revealing an inflammatory infiltrate. Twenty eight percent of the plasma cells contain immunoglobulins. The investigation of the immunoglobulin cell class pattern displays 8% IgA, 14% IgG and 6% IgM.

All cases of leukoplakias with dysplasia show an inflammatory infiltrate, whose density increases with higher grades of dysplasia. 53% of the plasma cells contain immunoglobulins: 15% IgA, 31% IgG, 7% IgM (Fig. 1a, b). The carcinomata display a dense cellular stromal reaction, which shows a positive correlation with the degree of differentiation. There is also a striking correlation between the differentiation of the carcinomata and the distribution of the inflammatory cells (Table 2). The percentage of plasma cells, especially IgG- and IgA-containing cells, increases with better differentiation of the carcinomata and decreases notably with progressive tumor dedifferentiation (Fig. 2a–c).

For the bleomycin-treated and irradiated cases our results are markedly different: After radiation the carcinomata appear less differentiated, show a very scanty inflammatory infiltrate, and a decrease in the number of plasma cells, especially IgG- and IgA-containing cells (Table 3).

In contrast after bleomycin-therapy the carcinomata are rather well differentiated and no distinct changes of the local humoral or cellular stromal reaction are present (Table 3).

In all cases of leukoplakia and carcinomata IgG and IgA can be demonstrated within and between the epithelial cells. The prickle cell layer is labelled in 76% of all cases whereas in leukoplakia without dysplasia the keratinized and

granular layer usually contains no immunoglobulins except in the superficially localized cells where a delicate IgG- and IgA-positive label is seen. The leukoplakias with dysplasia and carcinomata contain Ig-positive epithelial cells throughout all the epithelial layers.

Discussion

As a rule proliferating malignant tumor cells are accompanied by the infiltration of lymphocytes, plasma cells and macrophages. This so called "stromal reaction" has long been regarded as an indication of a host reaction against tumor invasion (Petersen, 1901; Russel, 1908; Ribbert, 1916). In many neoplastic diseases – more in epithelial than in mesenchymal – a positive correlation exists between the presence of a large lymphocytic stromal reaction and a favorable prognosis (see for review: Underwood, 1974; Berman, 1975). Similar observations have been reported from carcinomata in the oral cavity (Jones and Coyle, 1969; Paavolainen et al., 1973; Seifert and Burkhardt, 1977).

Some oral carcinomata develop from precancerous lesions, especially from leukoplakias with dysplasia (Burkhardt and Maerker, 1978). Considering the cellular stromal reaction to be a phenomenon of the immune surveillance of neoplasia (Burnet, 1970), we investigated its presence in precancerous and in the established tumor stages. In precancerous lesions one can generally assume that a more efficient cellular reaction will occur. The newly transformed cells may express a vigorous antigenicity and the response capacity of the host may be strong (Ioachim, 1976). Even severe dysplasias may regress or at least persist without evolution into tumors (Grundmann, 1975, 1976) and this persistance is usually associated with a vigorous stromal reaction. In established carcinomata the immune reaction of the host may have already become ineffective, due to an exhaustion of the immune capacity or to a selection of less antigenic tumor cell clones (Old et al., 1968; Klein, 1972; Klein, 1973).

In agreement with other investigations of leukoplakias (Kramer et al., 1970; Lehner, 1970, 1971; Burkhardt and Seifert, 1977) we found that the density of the stromal infiltrate is positively correlated with the grade of dysplasia. The analysis of the relative distribution of plasma cells, lymphocytes and macrophages reveals no significant changes between leukoplakias with and without dysplasia. Notable differences can be demonstrated by plasma cells; numbers of IgA- and IgG-positive cells increase significantly in leukoplakias with dysplasia.

Analysis of the carcinomata reveals that the number of plasma cells, especially IgA- and IgG-containing cells, is proportional to the degree of differentiation and to the amount of keratin. This correlation is supported by comparing carcinomata before and after radiation and bleomycin-therapy. After radiation the carcinomata show a progressive dedifferentiation, accompanied by a markedly lower cellular density of the stromal reaction and a decrease in plasma cells, in particular IgA- and IgG-positive cells. It is well known that radiation and some cytostatic drugs can influence the immunogenicity of tumors (Simmons et al., 1975) and the systemic and local immune reactivity of the host (Berdal

et al., 1975; Raben et al., 1976; Kapstad et al., 1978). Stjernswärd and Douglas (1977) found a considerable suppression of the lymphocyte-mediated cytotoxicity as late as 5 years after irradiation of breast and ovarian cancer. This immunosuppression was positively correlated to an accelerated appearance of distant metastases.

In contrast, bleomycin-treated carcinomata show a higher degree of differentiation (Prosoplasia: Schwalbe, 1911; Burkhardt et al., 1976) and display no significant changes in the local humoral and cellular immune reaction. These observations may also represent a stronger response of the host to a more highly differentiated tumor (Renault et al., 1972; Burkhardt and Höltje, 1975). Bleomycin-therapy does not alter the immune response of the host significantly, because this cytostatic drug produces only a very weak immunosuppressive effect (Boggs, 1974). There is evidence for an increased immunogenicity of tumors following bleomycin-therapy (Barduagni, 1976; Blomgreen et al., 1977).

The occurrence of mature plasma cells in association with tumors which are histogenetically distinct has already been described by other investigators (Berg, 1959: adenocarcinomata of the breast; Johansson and Ljungqvist, 1974; urothelial carcinomata; Martin et al., 1977: malignant melanoma). Squamous cell carcinomata with a high degree of differentiation are especially associated with plasma cell infiltrates (Ioachim, 1976; Viac et al., 1977; Bustamante et al., 1978) and some authors emphasize the prognostic importance of the plasma cell response. In low grade malignant skin tumors Viac et al. (1977) found numerous plasma cells secreting all immunoglobulin classes, whereas the infiltrate of highly malignant tumors was characterized by a reduced number of plasma cells which did not secrete all classes of immunoglobulin. Moreover, Hoepke (1954) and Berg (1959) observed that tumor cells seemed to be destroyed in the vicinity of the plasma cells. Adelstein et al. (1978) used a lymphocyte-cytotoxicity assay in patients with head and neck tumors and found notable lymphocyte-cytotoxicity to be correlated with a strong plasma-cellular stromal reaction.

Oral leukoplakias and carcinomata are also associated with a predominantly plasma cell infiltration (Löning et al., 1977). Our analysis of the stromal immunoglobulin distribution (increase in IgG and IgA) can be related to biochemical findings of saliva immunoglobulin changes in patients with oropharyngeal carcinomata (Brown et al., 1975; Wara et al., 1975; Niksic and Balogh, 1976). In these findings the IgA and IgG contents of the whole saliva of cancer patients were elevated, whereas no elevations were observed in the saliva of the parotid or submaxillary glands themselves. These biochemical results indicate a leakage of locally synthesized immunoglobulins through an altered oral mucosa. This is in accordance with our finding of the occurrence of immunoglobulin throughout all epithelial layers. The oral squamous epithelium contains mainly IgG, some IgA and virtually no IgM. It is of interest that in the normal oral mucosa the keratotic layer seems to act as a diffusion barrier and displays no detectable immunoglobulin except for a commonly observed superficial label (Brandtzaeg, 1975). Stromal immunoglobulins probably diffuse into the prickle cell layer, whereas saliva immunoglobulins penetrate the superficial keratinized cell layers.

In leukoplakia with dysplasia and carcinomata this diffusion barrier seems to be weakened. Lehner (1969) suggested that the epithelial immunoglobulins in patients with aphthous ulcers or Behcet's syndrome might represent autoantibodies which are bound to epithelial antigens and suggested a similar mechanism in oral leukoplakias and carcinomata (Lehner, 1973).

Mature plasma cells are associated with premalignant and malignant lesions of the oral mucosa, probably in response to specific antigenic stimulation. Certainly we cannot exclude that this is due, in part, to an increased mucosal permeability for exogenous antigens (Rognum et al., 1977). It seems less probable that the inflammatory infiltrate represents merely a reaction to infected or necrotic tissues as has been frequently suggested, because the responding cells are invariably plasma cells and lymphocytes, not polymorphonuclear leukocytes. Moreover, the correlation between the degree of tumor differentiation and the amount of the inflammatory infiltrate supports the assumption that the inflammatory cells are specifically attracted to the tumor by tumor-associated antigens (Ioachim, 1976).

Until recently T-cell mediated immunological recognition and destruction of tumors has been strongly emphasized. Recent observations on T-cell deficient nude mice, however, have challenged this concept (see for review: Stutman, 1976). Moreover, it is still a matter of controversy whether cytotoxicity of lymphocytes directed against tumor cells is of any importance in vivo (Underwood and Carr, 1972; Karesen, 1974; Underwood, 1976). The rejection of tumors has been frequently compared with the rejection of grafted tissues (Hoepke, 1954; Berg, 1959). Schlüter et al. (1973) analyzed the cellular infiltrate in chronic rejection of human kidney transplants and demonstrated that the plasma cell might act as an effector cell. The interrelationship between mature plasma cells and human tumors might also, therefore, be of importance. Immunoglobulins can neutralize free tumor antigens, bind complement, act directly on tumor cells and cooperate with a variety of blood borne cells causing immunologically specific target cell destruction (antibody dependent cell mediated cytotoxicity; Henney, 1977; Lewis et al., 1977). Under certain conditions, however, tumor-specific antibodies may block the lymphocyte-mediated cytotoxicity in vitro and possibly also in vivo by covering up tumor-associated antigenic determinants (humoral enhancement, Sjögren et al., 1972; Hellström and Hellström, 1976). On the other hand, recent investigations of suppressor cells demonstrated cellular enhancement mechanisms in cancer (Broder and Waldmann, 1978).

This study demonstrated that IgG- and IgA-containing plasma cells are consistently and characteristically associated with oral leukoplakias and carcinomata. The plasma cell density increases with tumor formation and is related to its degree of differentiation.

Our finding of a marked stromal and epithelial immunoglobulin reaction suggests that humoral factors play an important role in the tumor-host-interrelationship.

Acknowledgements. The authors gratefully acknowledge the skilful technical assistance of Miss M. Diekmann and Miss I. Brandt. This study was supported by a grant from the Deutsche Forschungsgemeinschaft.

References

Adelstein, E.H., Davis, W.E., Oxenhandler, R.W., Templer, J.W., Barrett, B.A.L.: Lymphocyte-tumor cell interaction in patients with head and neck cancer. The Laryngoscope **88**, 575–581 (1978)

Barduagni, A., Marolla, A., Calabresi, F., Terzoli, E.: Combined therapy with bleomycin and some immunological implications. Prog. Biochem. Pharmacol. **11**, 185–194 (1976)

Berdal, P., Iversen, O.H., Weyde, R.: Simultaneous intermittent bleomycin and radiological treatment of laryngeal cancer. Canad. J. Otolaryngol. **4**, 219–224 (1975)

Berg, J.W.: Inflammation and prognosis in breast cancer. Cancer (Philad.) **12**, 714–720 (1959)

Berman, L.D.: Immune parameters in the host response to neoplasia: morphological considerations. In: Immunity and cancer in man, Reif, A.E. (ed.), pp. 103–117. New York: Marcel Dekker Inc. 1975

Blomgreen, H., Edsmyr, F., Näslund, J.: Effect of bleomycin on peripheral lymphocytes. Acta Radiol. **16**, 325–336 (1977)

Boggs, S.S.: Minimal bone marrow damage in mice given bleomycin. Cancer Res. **34**, 1938–1942 (1974)

Brandtzaeg, P.: Immunoglobulin systems of oral mucosa and saliva. In: Oral mucosa in health and disease, Dolby, A.E. (ed.), pp. 137–213. Oxford-London-Edinburgh-Melbourne: Blackwell Scientific Publications 1975

Broders, A.C.: Squamous cell epithelioma of the lip. A study of 537 cases. J. Amer. Med. Ass. **74**, 656–664 (1920)

Broder, S., Waldmann, T.A.: The suppressor-cell network in cancer. New Engl. J. Med. **299**, 1335–1341 (1978)

Brown, A.M., Lally, E.T., Frankel, A., Harwick, R., Davis, L.W., Rominger, C.J.: The association of the IgA level of serum and whole saliva with the progression of oral cancer. Cancer (Philad.) **35**, 1154–1162 (1975)

Burkhardt, A., Höltje, W.-J.: The effects of intraarterial bleomycin therapy on squamous cell carcinomas of the oral cavity. Bioptic and autoptic examinations. J. Maxillofac. Surg. **3**, 217–230 (1975)

Burkhardt, A., Bommer, G., Gebbers, J.-O., Höltje, W.-J.: Riesenzellbildung bei Bleomycintherapie oraler Plattenepithelcarcinome. Enzymhistochemische, elektronenmikroskopische und ultrahistochemische Untersuchungen. Virchows Arch. A Path. Anat. and Histol. **369**, 197–214 (1976)

Burkhardt, A., Seifert, G.: Morphologische Klassifikation der oralen Leukoplakien. Dtsch. med. Wschr. **102**, 223–229 (1977)

Burkhardt, A., Maerker, R.: Dysplasieklassifikation oraler Leukoplakien und Präkanzerosen. Bedeutung für Prognose und Therapie. Dtsch. Z. Mund-Kiefer-Gesichts-Chir. **2**, 199–205 (1978)

Burkhardt, A.: Der Mundhöhlenkrebs und seine Vorstadien. Habilitationsschrift, Institut für Pathologie der Universität Hamburg (in prep.) (1979)

Burnet, F.M.: The concept of immunological surveillance. Prog. Exp. Tumor Res. **13**, 1–27 (1970)

Bustamante, R., Faure, M., Bejui, F., Thivolet, J.: Quantitative immunocytochemical study of plasma cells in skin tumoral stromal reaction. Eur. J. Cancer **14**, 1043–1050 (1978)

Grundmann, E.: Die Rolle der Lymphocyten bei der Wahrung der individuellen Integrität. In: Lymphocyt und klinische Immunologie, Theml, H., Begemann, H. (eds.), pp. 50–62. Berlin-Heidelberg-New York: Springer 1975

Grundmann, E.: Precancer-Histology. Trends and prospects. Z. Krebsforsch. **85**, 1–11 (1976)

Hellström, K.E., Hellström, I.: Immunologic enhancement of tumor growth. In: Mechanisms of tumor immunity, Green, I., Cohen, S., McCluskey, R.T. (eds.), pp. 147–174. New York-London-Sydney-Toronto: John Wiley and Sons 1976

Henney, C.S.: Mechanisms of tumor cell destruction. In: Mechanisms of tumor immunity, Green, I., Cohen, S., McCluskey, R.T. (eds.), pp. 55–86. New York-London-Sydney-Toronto: John Wiley and Sons 1976

Hoepke, H.: Wehrt sich der Körper gegen Geschwülste? Strahlentherapie **93**, 196–212 (1954)

Ioachim, H.L.: The stromal reaction of tumors: An expression of immune surveillance. J. Natl. Cancer Inst. **57**, 465–475 (1976)

Johansson, B., Ljungqvist, A.: Immunoglobulin-Lokalisation in Harnblasentumoren. Acta Path. Microbiol. Scand. Sect. A **82**, 559–563 (1974)

Jones, J.H., Coyle, J.I.: Squamous carcinomas of the lip: A study of the interface between neoplastic epithelium and the underlying mesenchyma. J. Dent. Res. **48**, 702–708 (1969)

Kapstad, B., Bang, G., Rennaes, S., Dahler, A.: Combined preoperative treatment with cobalt and bleomycin in patients with head and neck carcinoma–A controlled clinical study. Int. J. Radiat. Oncol. Biol. Phys. **4**, 85–89 (1978)

Karesen, R.: The immune reaction against malignant melanoma studied in a biopsy material. Acta Path. Microbiol. Scand. Sect. A **82**, 116–126 (1974)

Klein, E.: Tumour immunology: Escape mechanisms. Ann. Inst. Pasteur **122**, 593–602 (1972)

Klein, G.: Immunological surveillance against neoplasia. Harvey Lect. **69**, 71–102 (1973)

Kramer, I.R.H., El-Labban, N.G., Sonkodi, S.: Further studies on lesions of the oral mucosa using computer-aided analyses of histological features. Br. J. Cancer **29**, 223–231 (1974)

Lehner, T.: Pathology of recurrent oral ulceration and oral ulceration in Behcet's syndrome: Light, electron and fluorescence microscopy. J. Path. **97**, 481–494 (1969)

Lehner, T.: Cell mediated immune response in oral diseases: A review. J. Oral Path. **1**, 39–58 (1972)

Lehner, T., Wilton, J.M.A., Shillitoe, E.J., Ivanyi, L.: Cell-mediated immunity and antibodies to Herpesvirus hominis type 1 in oral leukoplakias and carcinomas. Br. J. Cancer **27**, 351–361 (1973)

Lewis, M.G., Phillips, T.M., Rowden, G., Jerry, L.M.: Humoral immune factors in metastasis in human cancer. In: Cancer invasion and metastasis: Biologic mechanisms and therapy, Day, S.B., Myers, W.P.L., Stansly, P., Garattini, S., Lewis, M.G. (eds.), pp. 245–258. New York: Raven Press 1977

Löning, Th., Burkhardt, A., Seifert, G., Gebbers, J.-O.: Zur Typisierung der Immunglobuline in oralen Leukoplakien und Karzinomen. Dtsch. Z. Mund-Kiefer-Gesichts-Chir. **1**, 168–177 (1977)

Martin, E.D., Rain, B., Brunaud, M.D., Cherrier, J.: Immunofluorescence study of plasmocytes in stromareaction of gastric carcinoma and narrowing mucosa. Abstracts VIth Congress of European Society of Pathology. London: 11.–17. Sept. (1977)

Niksic, M., Balogh, M.: Die Serum-Immunglobuline bei Patienten mit Malignomen des Kehlkopfs und des Rachens. Laryng. Rhinol. **55**, 882–887 (1976)

Old, L.J., Stockert, E., Boyse, E.A.: Antigenic modulation loss of TL antigens from cells exposed to TL antibody. Study of the phenomenon in vitro. J. Exp. Med. **127**, 523–539 (1968)

Paavolainen, M., Tarkkanen, J., Saksela, E.: Stromal reactions as prognostic factors in epidermoid carcinoma of the tongue. Acta Otolaryng. **75**, 316–317 (1973)

Petersen, W.: Beiträge zur Lehre vom Karzinom. Brun's Beitr. **32**, 543–654 (1901)

Pindborg, J.J., Renstrup, G., Poulsen, H.E., Silverman, S.: Studies in oral leukoplakia. V. Clinical and histological signs of malignancy. Acta Odont. Scand. **21**, 407–414 (1963)

Raben, M., Walach, N., Galili, U., Schlesinger, M.: The effect of radiation therapy on lymphocyte subpopulations in cancer patients. Cancer **37**, 1417–1421 (1976)

Renault, P., André, P., Laccourreye, H.: Cancers pharyngolaryngés traités par la bléomycin. Essai de controle histo-pathologique. Ann. Oto-Laryng. (Paris) **89**, 229–238 (1972)

Ribbert, H.: Heilungsvorgänge im Karzinom nebst Anregung zu seiner Behandlung. Dtsch. med. Wschr. **10**, 278–281 (1916)

Rognum, T.O., Baklien, K., Brandtzaeg, P.: The response pattern of immunoglobulin-producing cells in colon mucosa adjacent to carcinoma. Scand. J. Gastroenterol. **12** (Suppl. 45), 79 (1977)

Russel, B.R.: The nature of resistance to the inoculation of cancer. Third Scientific Report of the Imperial Cancer Research Fund **3**, 341–358 (1908)

Schlüter, E., Lennert, K., Bohle, A.: The immunologic significance of cellular infiltrates in chronic rejection of human kidney transplants. Virchows Arch. A Path. Anat. and Histol. **368**, 191–204 (1975)

Schwalbe, E.: Allgemeine Pathologie, pp. 238–239. Stuttgart: Ferdinand Enke 1911

Seifert, G., Burkhardt, A.: Neuere morphologische Gesichtspunkte bei malignen Tumoren der Mundschleimhaut. Dtsch. med. Wschr. **44**, 1596–1601 (1977)

Simmons, R.C., Rios, A., Toledo-Pereyra, L.H., Steinmuller, D.: Modifying the immunogenicity of cell membrane antigens, tumors and transplants. Am. J. Clin. Path. **63**, 714–734 (1975)

Sjögren, H.O., Hellström, I., Bansal, S.C., Warner, G.A., Hellström, K.E.: Elution of 'blocking factors' from human tumors, capable of abrogating tumor-cell destruction by specifically immune lymphocytes. Int. J. Cancer **9**, 274–283 (1972)

Stjernswärd, J., Douglas, P.: Immunosuppression and metastasis. In: Cancer invasion and metastasis: Biologic mechanisms and therapy, Day, S.B., Myers, W.P.L., Stansly, P., Garattini, S., Lewis, M.G. (eds.), pp. 319–331. New York: Raven Press 1977

Stutman, O.: Immunodeficiency and cancer. In: Mechanisms of tumor immunity, Green, I., Cohen, S., McCluskey, R.T. (eds.), pp. 27–53. New York-London-Sydney-Toronto: John Wiley and Sons 1976

Taylor, C.R.: The nature of Reed-Sternberg cells and other malignant 'reticulum' cells. Lancet **II**, 802–806 (1974)

Taylor, C.R.: Immunoperoxydase techniques. Arch. Path. Lab. Med. **102**, 113–121 (1978)

Underwood, J.C.E., Carr, I.: The ultrastructure of the lymphoreticular cells in non-lymphoid human neoplasms. Virchows Arch. Abt. B Zellpath. **12**, 39–50 (1972)

Underwood, J.C.E.: Lymphoreticular infiltration in human tumours. A review. Br. J. Cancer **30**, 538–546 (1974)

Underwood, J.C.E.: An ultrastructural analysis of lymphoreticular cell interactions in primary cultures of human non-lymphoid neoplasms and lymphomas. J. Path. **120**, 75–82 (1976)

Viac, J., Bustamante, R., Thivolet, J.: Characterization of mononuclear cells in the inflammatory infiltrates of cutaneous tumours. Br. J. Dermatol. **97**, 1–10 (1977)

Waldron, C.A., Shafer, W.G.: Leukoplakia revisited. A clinicopathologic study of 3256 oral leukoplakias. Cancer **36**, 1386–1392 (1975)

Wara, W.M., Amman, A.J., Wara, D.W., Phillips, T.L.: Serum IgA in the diagnosis of nasopharyngeal and paranasal sinus carcinoma. Radiology **116**, 409–411 (1975)

WHO Collaborating Centre for Oral Precancerous Lesions: Definition of leukoplakia and related lesions: An aid to studies on oral precancer. Oral Surg. **46**, 518–539 (1978)

Received February 19, 1979