Contact sensitivity reactions in the oral mucosa

Eva Elisabeth Ahlfors and Torstein Lyberg

Department of Pathology, Faculty of Dentistry, University of Oslo, and Research Forum, Ullevål University Hospital, Oslo, Norway

Ahlfors EE, Lyberg T. Contact sensitivity reactions in the oral mucosa. Acta Odontol Scand 2001;59:248–254. Oslo. ISSN 0001-6357.

Although the role of T cells in skin contact sensitivity (CS) immune reactions has been intensely studied, much less is known about the regulatory properties of T cells in the oral mucosa. Animal experiments have shown that hapten sensitization of the ectodermal oral mucosa leads to antigen-specific hypersensitivity reactions in the skin. Furthermore, oral mucosa or skin hapten sensitization resulted in CS inflammatory reactions in the oral mucosa on challenge. The oral mucosa CS responses were similar to those found skin with regard to cell phenotypes and cytokines. CS-like reactions were also found in the oral mucosa after exposure to an irritant detergent, sodium lauryl sulfate (SLS). The oral mucosa reacted at smaller SLS doses than did skin. Ions and molecules released from dental restorative materials (together with saliva and food and/or beverages) expose the gastrointestinal mucosa continuously over long time periods. From animal experiments we have learned that mice given antigen by gastric feeding, subsequently antigen-sensitized on skin, and finally elicited in the oral mucosa and in ear skin, showed tolerance in skin but gave simultaneous CS inflammatory reactions in the oral mucosa. Moreover, exposure of colon mucosa to antigen produced CS reactions in oral mucosa after challenge. Are there CS reactions in the oral mucosa? Clinical and experimental studies indicate that the oral mucosa can function both as induction and expression site of CS. The GI tract may be an important modifier of the CS inflammatory reactions seen in the oral mucosa. ☐ *Contact sensitivity; haptens; mouse and rat models; oral mucosa; T cells*

Eva Elisabeth Ahlfors, Department of Pathology and Section for Forensic Odontology, Faculty of Dentistry, P.O. Box 1109 Blindern, NO-0317 Oslo, Norway. Tel: +47 22 85 23 60, Fax: +47 22 85 23 51, e-mail: groea@odont.uio.no

The oral mucosa is exposed to a diversity of ingested and inhaled substances. An adequately active T-cell immune response of the oral mucosa is of paramount importance for the individual's health. Historically, the oral mucosa has been regarded as a body surface devoid of cellular elements able to express contact allergic reactions (1). Attempts to elicit systemic skin contact sensitivity (CS) immune reactions by sensitization of human oral mucosa resulted in immunological skin inflammatory T-cell reactions in only 7 of 17 subjects (2), indicating a diminished potential of the oral mucosa as an inductive site. These two studies raised important questions about T-cell defenses in the oral mucosa. First of all, will we find contact allergic T-cell reactions in the oral mucosa? Secondly, how do we segregate immunological T-cell responses in CS reactions from irritant/toxic reactions, as both types of inflammation have identical T-cell infiltrates and cytokine levels (3–7)? Additionally, does antigen exposure in the gastrointestinal tract influence T-cell reactions seen at oral mucosal sites?

The oral mucosa is an ectodermal tissue and can therefore be expected to have immunological properties similar to those of the skin. However, being a mucosal tissue and the initial segment of the endodermal digestive tract, antigen application on the oral mucosa may have the same downregulating effects on T-cell responses as seen after intestinal antigen exposure. Today, we have little knowledge of the links between the T-cell systems of skin, intestinal mucosa, and oral mucosa. For example, will manifestations of immunological T-cell reactions in the oral mucosa always be reflected by a positive epicutaneous patch test? Is there a link between skin and mucosal T cells?

T cells have been identified as dominating oral mucosal inflammatory infiltrates in several clinical conditions including lichenoid reactions, aphthous ulcers, psoriatic lesions, and systemic lupus erythematosus (8). These T cells are suggestive of cell-mediated immunity but also of irritant/toxic responses. Oral lichenoid reactions are often observed in the oral mucosa in close vicinity to dental restorative materials (such as fillings and prostheses) and/or orthodontic appliances, further emphasizing CS-like and/or irritant-like T-cell reactions on chronic exposure. Several studies have attempted to disclose a possible immunological CS etiology of lichenoid reactions by using epicutaneous patch tests (9–14). Diverse and inconsistent results have been reported. Indeed, if patch tests in patients with oral lichenoid reactions are negative, this could mean that CS was not the main pathogenic factor but also that the oral reaction had an irritant/toxic cause or that the skin patch test substance did not contain the allergen. Moreover, other substances in contact with the oral mucosa may modify the inflammatory responses in the tissue. Sodium lauryl sulfate (15, 16), which is known to increase mucosal and skin permeability, and triclosan (17, 18), which can have an immunosuppressive effect, represent such substances used in dental hygiene articles.

Although skin T-cell-dominated immune reactions have been intensively studied, much less is known about the regulatory properties of T cells in the oral mucosa. We

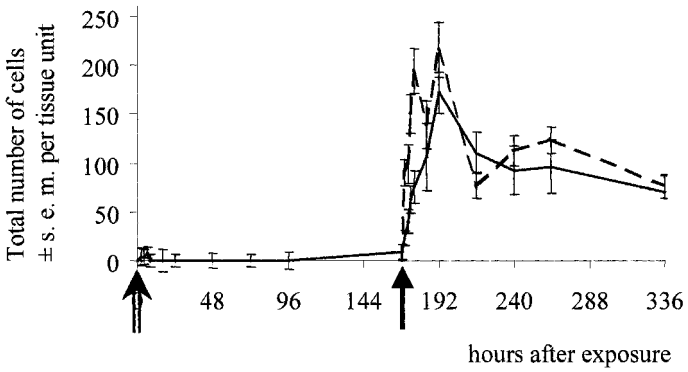

Fig. 1. Development of hapten-induced contact sensitivity reactions in the murine oral mucosa (see also Figs. 6A–E). Oral mucosa specimens were obtained from oral mucosa-sensitized (0–168 h) and elicited (168–336 h) animals. Animals with oral mucosal elicitation were either sensitized in the oral mucosa (unbroken line) or on skin (broken line), with the hapten oxazolone. Results are expressed as arithmetic mean specific increment in cell numbers per unit tissue ± standard error of the mean (s.e.m.)(vertical bars). Each experimental group consisted of 9 to 15 mice examined for each time point indicated. From Ahlfors & Czerkinsky (19); reprinted with permission from Clin Exp Immunol, Blackwell Science Ltd., Oxford, England.

have developed a rat and a mouse model for studies of CS reactions in the oral mucosa and of relations to similar reactions in other mucosal membranes and in the skin. We have also investigated irritant reactions caused by detergents, and, finally, we have studied the reactions of the oral mucosa and skin in animals preexposed to antigens in the upper or lower gastrointestinal tract, followed by sensitization and elicitation.

Oral mucosal CS reactions in animal models

Similarities of oral mucosa and skin CS reactions

To investigate T-cell reactions in the oral mucosa and compare them with the reactions at other mucosal and skin surfaces, we have hapten-sensitized rats or mice either in oral mucosa or in ear skin and subsequently hapten-elicited them at one of these sites. In these models we

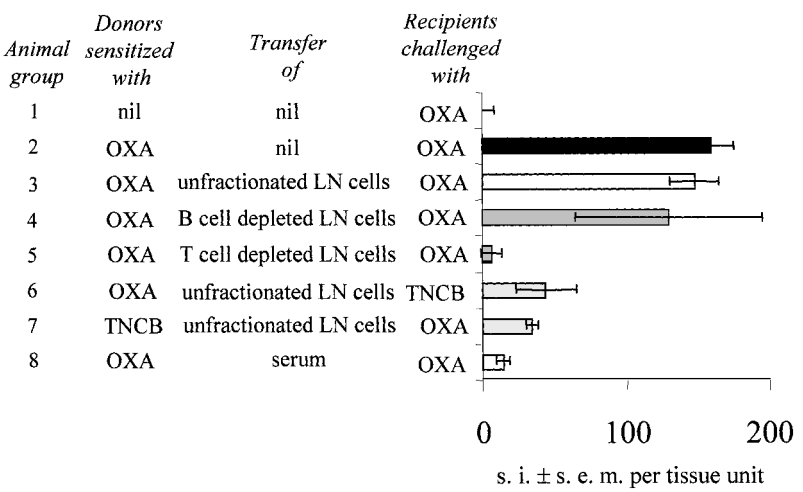

Fig. 2. Adoptive transfer of oral mucosa contact sensitivity (CS) reactions. Naïve C3H/HeN mice were challenged in the oral mucosa with hapten 5 days after transfer of lymph node (LN) cells or serum from hapten-sensitized cyclophosphamide-pretreated syngeneic donors. Oral mucosa CS reactions were evaluated 24 h after challenge. Results are expressed as arithmetic mean specific increment (s.i.) in cell numbers per unit tissue ± standard error of the mean (s.e.m.) (vertical bars). (Haptens were oxazolone (OXA) and trinitrochlorobenzene (TNCB).) From Ahlfors & Czerkinsky (19); reprinted with permission from Clin Exp Immunol, Blackwell Science Ltd., Oxford, England.

found specific antigen-elicited expression of CS inflammatory reactions in the oral mucosa of previously skin- or oral mucosa-sensitized animals (19, 20). The reactions showed a maximum intensity at 24–48 h (Figs. 1 and 6A–E). We observed that, as in skin, cellular infiltrates in the oral mucosa consisted mainly of T cells and macrophages (21). The T-cell nature of the reactions was established by adoptive transfer experiments; T-cell-containing lymph node cells from sensitized animals were given to naïve animals, and this entailed CS reactions on challenge, in contrast to serum transfer, which did not (Fig. 2) (19). Enzyme-linked immunosorbent assay (ELISA) analyses of extracts of tissue specimens showed increased interleukin (IL)-2 levels early in the sensitizing and in the eliciting phases, regardless of site of sensitization (skin or oral mucosa). This was in contrast to interferon (IFN)-γ, which was also seen early but only in the eliciting phase of both oral mucosa- and ear skin-challenged tissue (Ahlfors et al., unpublished observations). Furthermore, cells of oral mucosal epithelium were shown to have antigen-presenting capacity (22). Oral mucosal CS models in guinea pigs and hamsters have also been presented (23, 24). Rat oral mucosal CS reactions characteristically contained T cells and macrophages (25). Antigen-presenting capacities have been shown in oral epithelium Langerhans cells (LC) from human, rat, and mouse (26–29).

By and large, the oral mucosa reacts to antigen challenge in the same manner as the skin. This holds true both with regard to peak intensity of inflammation, infiltrating cell phenotypes, adoptive transfer experiments, cytokine profiles, and the antigen-presenting capacity of the oral mucosa compared with skin. With our current knowledge, we would conclude that ectodermal oral mucosa and skin display similar features in CS reactions.

Differences between oral mucosa and skin CS reactions

In spite of the similarities of the CS reactions in the oral mucosa and skin, several differences were found. We showed that the early oral mucosal inflammatory reactions in skin-sensitized mice had polymorphonuclear neutrophil (PMN)-rich infiltrates evident at 4 h and reaching a peak 8 h after challenge, whereas oral mucosa-sensitized mice had not (Figs. 3 and 6F and G) (21). Similar epidermal PMN-rich infiltrates were found in elicited skin, regardless of site of sensitization (skin or oral mucosa). In the epithelium of the oral mucosa, we observed $CD8^+$ cells that infiltrated the basal epithelial cell layer 48 h to 1 week after challenge, regardless of site of sensitization (oral mucosa or skin) (Figs. 4 and 6H). Importantly, this was not found in simultaneously elicited skin and suggested a possible late immunoregulation, specific to oral mucosa (21). Interestingly, $CD8^+$ cells were also found in the epithelium of the intestinal mucosa (30), which is of endodermal origin, in contrast to the epithelium of the oral mucosa, which is of ectodermal origin. This ELISA analysis showed 10 times higher IL-2 levels in the normal oral mucosa than in normal ear skin (Ahlfors et al., unpublished observations).

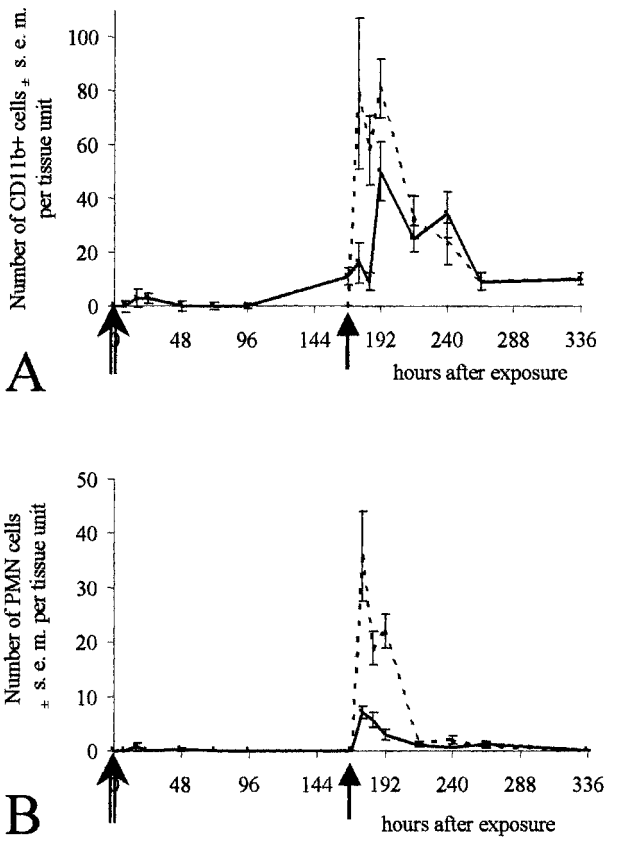

Fig. 3. 3A displays the kinetics of appearance of CD11b (Mac-1^+)-expressing macrophages and polymorphonuclear (PMN) leukocytes in oral mucosa contact sensitivity (CS) reactions. 3B shows PMN leukocytes (see also Fig. 6F and G). CS reactions were elicited in the oral mucosa (168–336 h) of mice sensitized on the abdominal skin (broken line) or in the oral mucosa (unbroken line) with oxazolone (OXA) (0–168 h). Data are expressed as mean numbers of $CD11b^+$ cells or PMN cells ± standard error of the mean (s.e.m.) per tissue unit, determined in six animals per experimental group at the indicated times. From Ahlfors et al. (21); reprinted with permission from Clin Exp Immunol, Blackwell Science Ltd., Oxford, England.

The oral mucosa retained the capacity to respond with CS reactions up to 5 weeks after sensitization in the oral mucosa, whereas after skin sensitization oral mucosal CS reactions decreased after 1 week and virtually disappeared by 3 weeks (19). Thus, oral sensitization led to especially prolonged oral delayed-type hypersensitivity (DTH)/CS.

Oral mucosal irritant reactions in animal experiments

The anionic irritant sodium lauryl sulfate (SLS) (present in most brands of toothpaste) is considered to elicit irritant reactions when applied to skin (31). Many studies have focused on distinguishing CS and irritant reactions with regard to both cell phenotypes (3) and cytokines (4–7)

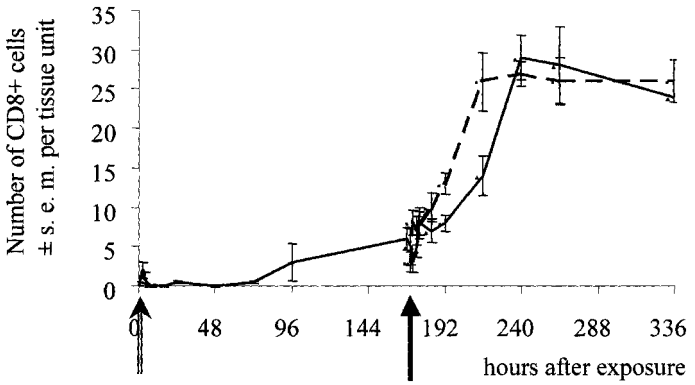

Fig. 4. The kinetics of appearance of $CD8^+$ cells in oral mucosa contact sensitivity reactions (see also Fig. 6H). The animals were sensitized with oxazolone at 0 h in the oral mucosa, and the reaction was followed up for 0–168 h. The oral mucosa was then elicited at 168 h, and the reactions were followed up for 336 h (unbroken line). Other mice were sensitized on abdominal skin and then elicited in the oral mucosa (broken line). From Ahlfors et al. (21); reprinted with permission from Clin Exp Immunol, Blackwell Science Ltd., Oxford, England.

released during any of those reactions but have failed. In our animal models we have found that the oral mucosa is much more sensitive to low concentrations of SLS than skin (32). After exposure of the oral mucosa to 2% SLS, superficial epithelial necrosis and 6-h PMN infiltrations were observed. At 24–48 h the epithelium had recovered, and the inflammatory reactions were mononuclear, similar to what is seen in a CS inflammatory infiltrate. SLS administration on the oral mucosa decreased the concentrations of hapten needed to induce inflammatory reactions, not only locally in the oral mucosa but also systemically in untreated skin (33).

The increased mucosal reactivity seen in animal experiments on SLS exposure is in line with experiments using the water-soluble hapten trinitrobenzene sulfonic acid (TNBS) in plastic chambers on skin surfaces (34). Here the humid environment enabled the 'large' hapten to penetrate the epidermis and cause sensitization. Such penetration and ensuing reaction was not seen after exposure of dry skin to TNBS (34). The easier penetration of smaller and larger molecules into oral mucosal membranes might lead to activation of T cells and release of inflammatory mediators. Would this in turn increase the risk of becoming sensitized to exposing haptens or other substances in contact with the oral mucosa?

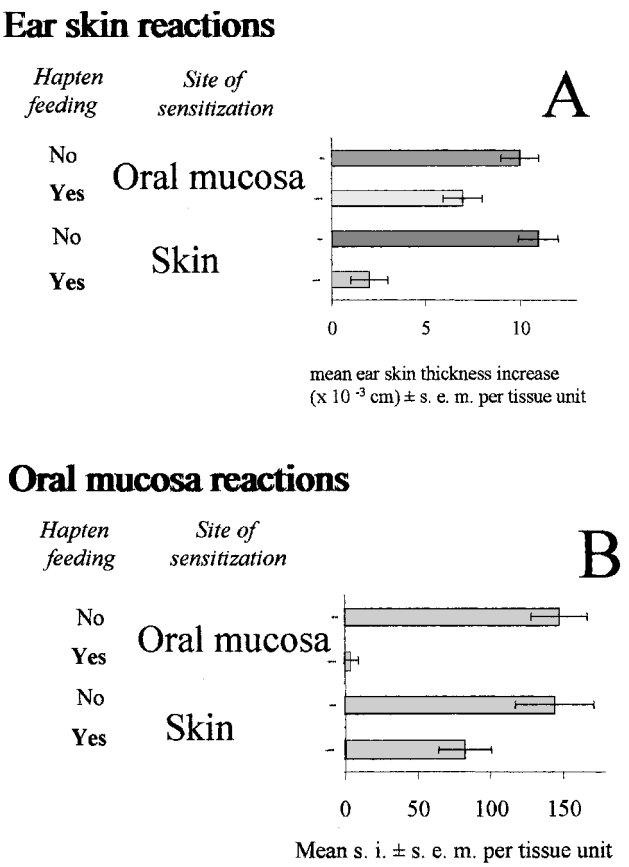

Fig. 5. Intragastric administration of trinitrobenzene sulfonic acid suppressed trinitrochlorobenzene skin-induced but not oral mucosa-induced cutaneous contact sensitivity (CS) reactions (A) and oral mucosa-induced but not skin-induced oral mucosa CS reactions (B). Data are expressed as (A) mean ear swelling ± standard error of the mean (s.e.m.) and (B) mean specific increment (s.i. ± s. e. m.) in cell nuclei counts per tissue unit determined in groups of six animals. From Ahlfors & Czerkinsky (39); reprinted with permission from Scand J Immunol, Blackwell Science Ltd., Oxford, England.

T-cell immune reactions involving the gastrointestinal (GI) tract

Food, beverages, and other enterally fed foreign substances are metabolized in the GI tract into smaller molecules, which can pose as antigens. A clinical example of T-cell reactions taking place at GI surfaces is Crohn disease with ongoing $CD4^+$ Th1 responses and release of IL-12, IFN-γ, and tumor necrosis factor (TNF)-α (35). In

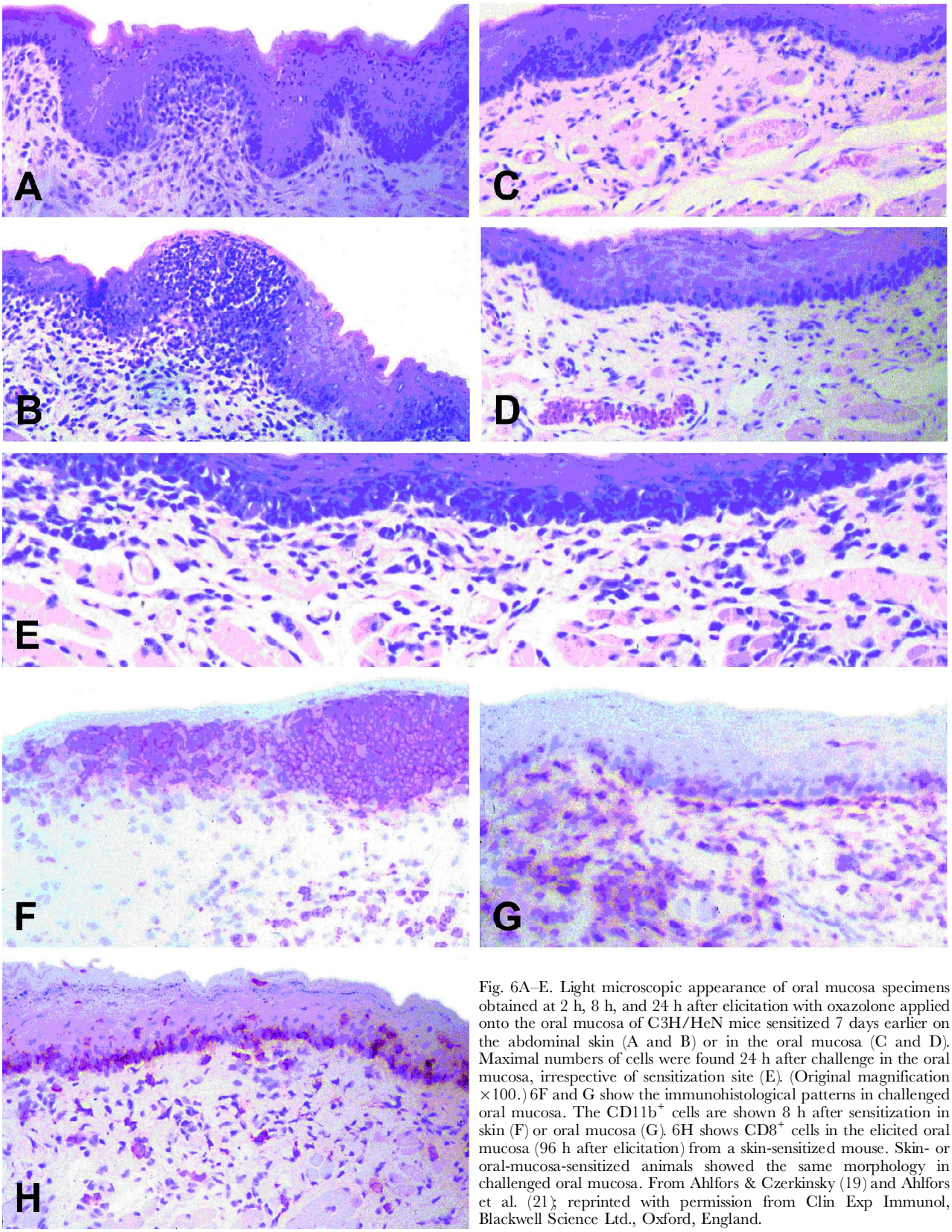

Fig. 6A–E. Light microscopic appearance of oral mucosa specimens obtained at 2 h, 8 h, and 24 h after elicitation with oxazolone applied onto the oral mucosa of C3H/HeN mice sensitized 7 days earlier on the abdominal skin (A and B) or in the oral mucosa (C and D). Maximal numbers of cells were found 24 h after challenge in the oral mucosa, irrespective of sensitization site (E). (Original magnification ×100.) 6F and G show the immunohistological patterns in challenged oral mucosa. The $CD11b^+$ cells are shown 8 h after sensitization in skin (F) or oral mucosa (G). 6H shows $CD8^+$ cells in the elicited oral mucosa (96 h after elicitation) from a skin-sensitized mouse. Skin- or oral-mucosa-sensitized animals showed the same morphology in challenged oral mucosa. From Ahlfors & Czerkinsky (19) and Ahlfors et al. (21); reprinted with permission from Clin Exp Immunol, Blackwell Science Ltd., Oxford, England.

experimental murine CS models, antigens like ovalbumin and TNBS were introduced into the GI tract through enemas (36). Peripheral systemic DTH tolerance could be induced by giving the contact antigen enterally (37, 38). Similar downregulation of systemic skin CS responses could be induced after oral mucosa exposure to antigen (27, 28). In our mouse model we found that hapten feeding suppressed skin-induced but not oral mucosa-induced cutaneous CS reactivity (Fig. 5A) (39). Vice versa, hapten feeding suppressed oral mucosa-induced but not skin-induced CS responses in the oral mucosa (Fig. 5B) (39). The suppression of CS in the oral mucosa was associated with decreased infiltration of macrophages and $CD4^+$ T cells and virtually no $CD8^+$ T cells (39). In pilot mouse experiments we have, after sensitization with TNBS in the colon, found local $CD4^+$ T-cell-rich inflammatory reactions in the oral mucosa elicited with the TNBS cross-reactive hapten TNCB (trinitrochlorobenzene).

These initial studies of GI exposure, followed by sensitization and elicitation with haptens, indicate that the oral mucosa possesses powerful regulatory abilities with regard to T-cell immune reactions. Apparently, with the antigens used here, oral tolerance is broken either by a sensitizing or by an eliciting phase in the oral mucosa. The factors, which regulate the development of such inflammatory responses, have not yet been identified. One may speculate that the oral mucosa, being the ectodermal entrance of the endodermal intestinal mucosa, breaks oral tolerance induced by feeding due to intrinsic factors in the ectodermal tissue in this location. Whether these factors influence effector or suppressor cells and/or cytokines such as IL-12, IFN-γ, or IL-10, transforming growth factor (TGF)-β remains to be explored. Additionally, locally expressed adhesion molecules may distinguish cell access to the oral mucosa. However, the picture is complicated by the fact that oral tolerance is not broken when the oral mucosa is sensitized and elicited after feeding. The results may perhaps explain why lichenoid reactions occur 10 times more frequently in the oral mucosa than in skin. We suggest that the value of skin patch testing in cases of suspected oral mucosal CS reactions should be questioned.

Better knowledge of effector mechanisms and the regulatory aspects of T cell-reactions in oral mucosa, other mucosal membranes, or skin are important to prevent these types of reactions from occurring and to find adequate therapies by appropriate T-cell-directed manipulations.

References

1. Nyquist G. A study of denture sore mouth: an investigation of traumatic, allergic and toxic lesions of the oral mucosa arising from the use of full dentures [thesis]. Acta Odontol Scand 1952;10 Suppl 9.
2. Lowney ED. Immunologic unresponsiveness to a contact sensitizer in man. J Invest Dermatol 1968;51:411–7.
3. Ranki A, Kanerva L, Førstrøm L, Konttinen Y, Mustakallio KK. T and B lymphocytes, macrophages and Langerhans cells during the course of contact allergic and irritant reactions in man. Acta Derm Venereol 1983;63:376–83.
4. Brand CU, Hunziker T, Yawalkar N, Braathen LR. IL-1 beta protein in human skin lymph does not discriminate allergic from irritant contact dermatitis. Contact Dermatitis 1996;35:152–6.
5. Tsuruta J, Sugisaki K, Dannenberg AM Jr, Yoshimura T, Abe Y, Mounts P. The cytokines NAP-1 (IL-8), MCP-1, IL-1 beta, and GRO in rabbit inflammatory skin lesions produced by the chemical irritant sulfur mustard. Inflammation 1996;20:293–318.
6. Hoefakker S, Caubo M, van't Erve EH, Roggeveen MJ, Boersma WJ, van Joost T, et al. In vivo cytokine profiles in allergic and irritant contact dermatitis. Contact Dermatitis 1995;33:258–66.
7. Kondo S, Pastore S, Shiviji GM, McKenzie RC, Sauder DN. Characterization of epidermal cytokine profiles in sensitization and elicitation phases of allergic contact dermatitis as well as irritant contact dermatitis in mouse skin. Lymphokine Cytokine Res 1994;13:367–75.
8. Sanchez R, Jonsson R, Ahlfors E, Backman K, Czerkinsky C. Oral lesions of lupus erythematosus patients in relation to other chronic inflammatory oral diseases: an immunologic study. Scand J Dent Res 1988;96:569–78.
9. Takeuchi Y, Iwase N, Suzuki M, Tsuyuki S. Lichen planus with involvement of all twenty nails and the oral mucous membrane. J Dermatol 2000;27:94–8.
10. McGivern B, Pemberton M, Theaker ED, Buchanan JA, Thornhill MH. Delayed and immediate hypersensitivity reactions associated with the use of amalgam. Br Dent J 2000;188:73–6.
11. Koch P, Bahmer FA. Oral lesions and symptoms related to metals used in dental restorations: a clinical, allergological, and histological study. J Am Acad Dermatol 1999;41:422–30.
12. Bergdahl J, Tillberg A, Stenman E. Odontologic survey of referred patients with symptoms allegedly caused by electricity or visual display units. Acta Odontol Scand 1998;56:303–7.
13. Tosti A, Piraccini BM, Peluso AM. Contact and irritant stomatitis. Semin Cutan Med Surg 1998;16:314–9.
14. Hochman N, Zalkind M. Hypersensitivity to methyl methacrylate: mode of treatment. J Prosthet Dent 1997;77:93–6.
15. Healy CM, Cruchley AT, Thornhill MH, Williams DM. The effect of sodium lauryl sulphate, triclosan and zinc on the permeability of normal oral mucosa. Oral Dis 2000;6:118–23.
16. Fartasch M, Schnetz E, Diepgen TL. Characterization of detergent-induced barrier alterations—effect of barrier cream on irritation. J Invest Dermatol Symp Proc 1998;3:121–7.
17. Mustafa M, Bakhiet M, Wondimu B, Modeer T. Effect of triclosan on interferon-gamma production and major histocompatibility complex class II expression in human gingival fibroblasts. J Clin Periodontol 2000;27:733–77.
18. Skaare AB, Kjærheim V, Barkvoll P, Rolla G. Does the nature of the solvent affect the anti-inflammatory capacity of triclosan? An experimental study. J Clin Periodontol 1997;24:124–8.
19. Ahlfors E, Czerkinsky C. Contact sensitivity in the murine oral mucosa. I. An experimental model of delayed type hypersensitivity at mucosal surfaces. Clin Exp Immunol 1991;86:449–56.
20. Ahlfors E, Larsson P. Light microscopic study of experimental cell-mediated immunity in rat oral mucosa. Scand J Dent Res 1984;92:549–56.
21. Ahlfors E, Jonsson R, Czerkinsky C. Experimental T cell-mediated inflammatory reactions in the murine oral mucosa. II. Immunohistochemical characterization of resident and infiltrating cells. Clin Exp Immunol 1996;104:297–305.
22. Eriksson K, Ahlfors E, George-Chandy A, Kaiserlian D, Czerkinsky C. Antigen presentation in the murine oral epithelium. Immunology 1996;88:147–52.
23. Adams D, Williamson JJ, Dolby AE. Delayed hypersensitivity response in guinea pig oral mucosa. J Pathol 1969;97:495–501.
24. Mohammad AR, Mincer HH. Dinitrochlorobenzene contact hypersensitivity in the hamster cheek pouch. J Oral Pathol 1976;5:169–74.

25. Warfvinge G, Larsson Å. Immunocytochemical analysis of early focal cellular infiltrates in experimental oral contact hypersensitivity. Acta Derm Venereol 1991;71:377–83.
26. Hasséus B, Dahlgren U, Bergenhotz G, Jontell M. Antigen presenting capacity of Langerhans cells from rat oral epithelium. J Oral Pathol Med 1995;24:56–60.
27. van Wilsem EJG, van Hoogstraten I, Bréve J, Zaman Y, Kraal G. In vivo antigen presentation capacity of dendritic cells from oral mucosa and skin draining lymph nodes. Adv Exp Med Biol 1994;355:63–7.
28. van Wilsem EJ, van Hoogstraaten IM, Bréve J, Scheper RJ, Kraal G. Dendritic cells of the oral mucosa and the induction of oral tolerance. A local affair. Immunology 1994;83:128–32.
29. Barett AW, Ross DA, Goodacre JA. Purified human oral mucosal Langerhans cells function as accessory cells *in vitro*. Clin Exp Immunol 1993;92:158–63.
30. Kim SK, Reed DS, Heath WR, Carbone F, Lefrancois L. Activation and migration of CD8 T cells in the intestinal mucosa. J Immunol 1997;159:4295–306.
31. Effendy I, Maibach HI. Surfactants and experimental irritant contact dermatitis. Contact Dermatitis 1995;33:217–25.
32. Ahlfors EE, Warfvinge G, Larsson PÅ. Toxic lesions in rat oral mucosa: toxic thresholds and sensitizing propensity of DNFB and SLS in a rat model [abstract]. Swed Dent J 1986;6:254.
33. Warfvinge G, Ahlfors EE, Larsson PÅ. Toxic lesions in rat oral mucosa: the early stages of SLS-induced lesions, a time sequence study [abstract]. Swed Dent J 1986;6:254.
34. Shimizu T, Munn CG, Streilein JW. Transepidermal induction of contact hypersensitivity in mice with a water-soluble hapten. J Invest Dermatol 1993;101:749–53.
35. MacDonald TT, Monteleone G, Pender SL. Recent developments in the immunology of inflammatory bowel disease. Scand J Immunol 2000;51:2–9.
36. Boirivant M, Fuss IJ, Ferroni L, De Pascale M, Strober W. Oral administration of recombinant cholera toxin subunit B inhibits IL-12-mediated murine experimental (trinitrobenzene sulfonic acid) colitis. J Immunol 2001;166:3522–32.
37. Tomasi T. Oral tolerance. Transplantation 1980;29:353–6.
38. Marth T, Ring S, Schulte D, Klensch N, Strober W, Kelsall BL, et al. Antigen-induced mucosal T cell activation is followed by Th1 T cell suppression in continuously fed ovalbumin TCR-transgenic mice. Eur J Immunol 2000;30:3478–86.
39. Ahlfors E, Czerkinsky C. Suppression of delayed-type hypersensitivity in the murine oral mucosa by prior intragastric administration of hapten. Scand J Immunol 1997;46:268–73.