Host factors affecting oral candidiasis

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Candida species are responsible for a wide range of systemic as well as superficial opportunistic infections, which are of particular importance among debilitated and immunocompromised patients. Species of the genus *Candida* comprise part of the oral commensal microflora of healthy individuals, with *Candida albicans* being the most common pathogen of the genus. A diverse array of host factors has been implicated in the pathogenesis of oral candidiasis. This paper describes the local, systemic and iatrogenic factors affecting oral candidiasis.

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Introduction

Candida species are normal oral commensals[1] found in 17-75% of healthy individuals and most debilitated people.[2,3] The transition of this innocuous commensal to the disease-causing 'parasite' may be associated with the virulence attributes of the microorganism.[1]

A diverse array of local and systemic factors has been implicated in the pathogenesis of oral candidiasis.[1] These factors act in concert and the eventual outcome of these disease processes is frequently related to the superimposition of the local factors upon systemic factors or vice versa. Host factors are of critical importance in the development of the disease state and *Candida* species are strictly opportunistic pathogens that mainly cause disease when the host defences are inadequate.[1] The interactions between *Candida* and the host are extremely complex, involving host factors, systemic factors and iatrogenic factors.

Local host factors that predispose to oral candidiasis

Mucosal barrier

For *Candida* species to establish an infective process, the organisms must adhere to a host surface, proliferate and penetrate the first line of the host's defence which is the keratinised or non-keratinised oral mucosa. The proteins present in these mucosal cells may act as antifungals and retard candidal invasion.[4] Changes in the epithelium of the oral mucosa, atrophy, hyperplasia or dysplasia, may affect the efficiency of the mucosal barrier.[1] It is possible for the superficial mucosa to protect the host against *Candida* because constant desquamation of the mucosa takes place at a rate greater than *Candida* growth.[1]

Organisms can protect themselves from being sloughed off the surface of the mucosa either by the production of secretions and fluids or the movement of food or by attaching in a specific manner.[5] When attachment takes place on solid surfaces, the organisms benefit from the enriched nutrient status that exists at the solid-liquid interfaces.[6] Furthermore, changes in surface protein glycosylation may expose hydrophobic protein structures on the surface of the cell,[7] which affects adherence properties. Changes in the surface of yeast cells may be caused by *Candida*-host interactions. For example, adherence to human buccal epithelial cells induces the synthesis of new proteins in *Candida albicans* and the expression of signal proteins.[8] An understanding of adherence mechanisms, the signals they generate and the processes they induce, may therefore lead to specific preventive treatments for individuals predisposed to candidiasis.[9]

In vitro studies show that changing environmental conditions can induce morphogenesis of *C. albicans*[10] and that the cell surface of the hyphal form of *C. albicans* displays a number of proteins that are either absent or masked in the yeast form.[11,12] The hyphal form also exhibits increased adherence properties[13-15] which appear to correlate with increased expression of the $\alpha 5\beta 1$-like fibronectin receptor in cells forming hyphae.[16]

Saliva

A continuous flow of saliva is important in preventing oral colonisation by *Candida* because it removes the unattached or loosely attached *Candida* from the oral cavity.[1] Saliva flow rate[9] as well as the quantity and the quality of the saliva[1] affect microbial clearance. Qualitative changes in saliva such as the content of salivary glucose may also influence the oral carriage of *Candida*.[1] Glucose may be a prime factor in the predisposition of diabetics to candidiasis as shown by in vitro experiments which demonstrated minimal or no growth of *Candida* species in saliva but when supplemented with glucose, saliva fostered the multiplication of yeasts.[17-19] Furthermore, the secretory IgA component of saliva aggregates yeasts and assists in clearance,[20,21] thus inhibiting candidal adhesion to host surfaces.[1] Saliva also contains antifungal factors such as lysozyme, lactoperoxidase, lactoferrin and histidine-rich polypeptides, which may help to keep the oral *Candida* populations under control.[1]

Oral carriage of *Candida* species and coliforms is significantly higher among patients with burning mouth syndrome and this may be directly or indirectly related to reduced salivary gland function in this group.[22,23] A similar increase in oral carriage of *Candida* has also been demonstrated in patients undergoing cytotoxic or irradiation therapy.[24] Coliforms are regarded as transient oral colonisers that are usually found in small numbers among oral commensals.[23] However, in the above situations they constitute an integral component of resident commensals.

The coliforms may further promote *Candida* colonisation of epithelia because the yeasts co-adhere preferentially to coliforms, for example *Klebsiella* species, than to epithelial surfaces.[25,26] Therefore, a higher prevalence of yeasts observed in the abovementioned patient groups could be a secondary phenomenon while the primary colonisation of the oral cavity is facilitated by coliforms.[1]

Salivary pH is another factor that may influence oral *Candida* carriage. There is a correlation between high carriage and low salivary pH on the dorsum of the tongue,[27] under maxillary dentures[1] and in the oral cavity.[1,28] A possible mechanism whereby low pH conditions may promote oral colonisation is the superior ability of yeasts to adhere to epithelia and denture acrylic surfaces at a low pH of approximately 2 to 4.[14,29] Another mechanism may be the aciduric and acidophilic nature of *Candida* species which allow them to thrive in a low pH milieu.[10]

Phagocytes

Phagocytes provide the second line of defence against invasive *Candida* infection.[9] In the immunocompetent host, neutrophils, eosinophils and monocytes phagocytose yeast cells whereas the hyphal forms of *C. albicans* gain access to deeper tissues.[30] During the acute inflammatory responses to *Candida* infection, neutrophils predominate. Intracellular killing of *Candida* involves both oxidative and non-oxidative mechanisms.[31] Granulocytes and macrophages require augmentation by cytokines such as interferon-gamma, granulocyte-macrophage colony-stimulating factor, and interleukin-1 and -2, produced by T cells for maximum killing efficiency.[31,32] A significant factor in the pathogenicity of *C. albicans* is the ability of surface molecules, such as mannoproteins and complement receptors, to modulate phagocyte responses.[31] The importance of cell-mediated immunity in resistance to *Candida* infection is illustrated by the severe mucosal candidiasis seen with T cell dysfunction in AIDS patients and in many people with chronic mucocutaneous candidiasis.[10]

Morphogenesis

C. albicans can grow in a number of morphological forms, ranging from yeast to hyphae.[9] Pseudohyphal forms are found. This morphology can also be assumed by several other *Candida* species as well.[10] There is a belief that the hyphae are the invasive and pathogenic form, while the vegetative yeast is the commensal non-pathogenic form. Evidence for this is, however, equivocal.[10,33] Sherwood *et al.*[34] demonstrated that hyphae are capable of contact-sensing or thigmotropism. *C. albicans* hyphae incubated on perforated filters on agar plates grew through the pores and along the grooves of the filters. This property could facilitate the penetration of some tissues. Some *C. albicans* strains exhibit switching of colony morphology when nutritionally stressed which is accompanied in some cases by chromosomal translocation.[35] This phenotypic switching may be a genetic mechanism that allows asexual *C. albicans* to adapt to environmental change.[35]

Systemic factors which predispose to oral candidiasis

Immunocompromised individuals

The mechanisms that protect the human host against fungal infection depend upon a combination of factors. In the immunocompromised patient, alterations in phagocytic or lymphocytic cell numbers or function are often the most critical factors predisposing to fungal infection.[36]

Diabetes and oral candidiasis

Although oral candidiasis is prevalent among diabetics, the mechanism which predisposes these individuals to high oral carriage of this organism is not clear.[1] It is accepted that high salivary glucose levels among diabetics favour the growth of yeasts.[17,37] However, some investigators have not been able to show a relationship between glycaemic control and oral carriage.[38,39] It seems that defects in *Candida*-cidal activity of neutrophils, particularly in the presence of glucose may promote oral carriage of *Candida* among diabetics.[40] Furthermore, Farman and Nutt[41] have found microvascular degeneration in capillaries within the lamina propria with atrophic candidal glossitis in diabetics which might promote carriage and infection.

The adhesion of *Candida* to buccal epithelial cells obtained from diabetics was significantly higher ($p<0.001$; 55% increase) than to cells obtained from non-diabetic controls[42]. This implies that there may be intrinsic qualitative changes on the cell surface receptors modulating yeast adhesion in diabetes.[1,42]

HIV and oral candidiasis

Oropharyngeal candidiasis is the most common fungal infection among patients infected with HIV.[43-45] *C. albicans* strains are the prevailing species causing oral candidiasis among patients with HIV infection[46-48] and are identical to the commensal organisms found in healthy individuals.[49]

Oral candidiasis is one of the earliest indictors of the progression to AIDS.[9] It becomes clinically apparent in the prodromal stages of AIDS[50] with more than 75% of infected patients presenting with candidiasis during the course of the disease.[51] Oesophageal candidiasis among AIDS patients can be extensive.[52] This high frequency of oral *Candida* carriage[51,53] and candidiasis among HIV-seropositive and AIDS patients emphasises that a fully-functional immune system is needed to prevent candidiasis.

Leukaemia and lymphoma

Systemic candidiasis associated with malignancies, particularly leukaemias and lymphomas, is well documented.[10] This stems partly from therapeutic measures such as cytotoxic and immunosuppressive drugs and radiotherapy which are essential in the treatment of many malignancies. Concurrent administration of antibiotics is also relevant in this context.[1,40] These conditions are also associated with characteristic defects of phagocytic or lymphocytic cell numbers or function.[54] The remaining neutrophils have metabolic defects which result in impaired migration and microbicidal function. Furthermore, treatment leads to profound neutrophil depletion and deficient T- and B-cell function, which persist until remission is attained.

Altered nutritional states

Nutritional factors act in concert with a number of co-factors in the pathogenesis of oral candidiasis[55]. Amongst others, iron and vitamin deficiency have been investigated and probably influence the disease process via systemic pathways.

Iron deficiency

Iron deficiency may produce an impairment of iron-dependent enzyme systems, thereby affecting the metabolism and, hence, the kinetics of the rapidly dividing oral epithelial cells.[56] Such alterations may result

in the epithelial surface becoming more conducive to the adhesion, growth and invasion of *Candida*. Iron deficiency may also substantially depress the cell-mediated immune response.[57] Other general effects of iron deficiency may include impaired phagocytosis and inadequate antibody production.[58,59] The association between oral candidiasis and iron deficiency was first described by Cawson.[60] A high prevalence of candidal infection in iron-deficient patients with angular cheilitis and atrophic glossitis has also been reported.[61] Iron deficiency may result in persistent chronic mucocutaneous candidiasis which is difficult to eradicate while the iron deficiency remains.[62]

Vitamin deficiency

Folate deficiency has been reported to cause degenerative changes in the oral mucosa.[63] The latter possibly contributes to the pathogenesis of oral candidiasis by providing a less hostile surface for candidal colonisation.

Iatrogenic factors that predispose the host to infection

Antibiotic therapy

Antibiotic treatment can cause *C. albicans* overgrowth in the oral cavity by eliminating competing microorganisms and exposing additional sites suitable for colonisation.[9] Broad-spectrum antibiotic therapy e.g. tetracycline, rather than narrow-spectrum antibiotics, is generally accepted as one of the more common iatrogenic factors which initiate oral candidiasis.[1]

Corticosteroid therapy

Corticosteroids have potent anti-inflammatory and immunosuppresive properties.[1,36] These drugs can lower host resistance to infection and predispose individuals to systemic and superficial candidiasis.[1] Dennis and Itkin[64] were the first to draw attention to the relationship between steroid inhalers and oral candidiasis. The synthetic steroids, beclomethasone dipropionate, betamethasone valerate, sodium cromoglycate and triamcinolone acetonide, used to treat asthma, are also associated with oral and pharyngeal candidiasis.[65]

The mechanisms whereby inhaled or systemic steroids predispose to oral candidiasis have as yet not been fully clarified. Treatment with these drugs leads to a marked reduction in neutrophil migration, resulting in suppression of inflammation, associated with impaired neutrophil phagocytic and microbiocidal function. Furthermore, treatment with corticosteroids leads to a profound, but transient reduction in the number of circulating T and B cells.[66] Although corticosteroids do not abolish lymphokine production by activated T cells, the response of macrophages to these mediators is often reduced or destroyed. Also, patients treated with corticosteroids have a high level of salivary glucose which may promote growth, proliferation and adhesion of *Candida*.[17]

Cytotoxic therapy and radiotherapy (irradiation)

Opportunistic oral candidiasis is commonly observed in patients who are on cytotoxic treatment and radiotherapy. *Candida* species are responsible for approximately half the oral infections that occur during anti-leukaemia chemotherapy and almost two-thirds of those among patients given antineoplastic drugs for solid tumours.[67] Irradiation affects both the specific and non-specific elements of host protection against infection. The epithelial barrier of the mouth and gastrointestinal tract will often be damaged, but myelosuppression is often the major factor leading to infectious complications. Irradiation also affects most aspects of T and B cell function, resulting in profound suppression of cell-mediated and humoral immunological reactions.[36] Carriage of oral *Candida* increases during radiotherapy for oral and laryngeal cancer[68] and cytotoxic therapy for solid tumours of oral and perioral regions.[69]

Cigarette/tobacco smoking

The mechanisms whereby *Candida* carriage and metabolism may be affected, by cigarette or cigar smoke, are uncertain. Arendorf and Walker[27] proposed that smoking may lead to localised epithelial alterations which facilitate colonisation. An alternative hypothesis is that cigarette smoke contains nutritional factors that *C. albicans* uses readily.[1] Aromatic hydrocarbons in cigarette smoke may be converted by inducible enzyme systems in *Candida* species to carcinogen end-products. This, together with the observation that *C. albicans* can catalyse the formation of N-nitrosobenzyl-methylamine, may partly explain why *Candida*-associated leucoplakia has a higher potential for malignant change than other leucoplakias.[1]

Conclusion

No single factor but rather a combination of different factors appears to be responsible for the pathogenicity of *C. albicans* (Table 1). Dental professionals should be aware that local host factors not only influence colonisation but also the form of *Candida* infection that is likely to become established.

Table 1: Host factors and their effects on oral candidiasis

Host factor	Effect on *Candida* growth
Local factors	
Mucosal barrier	
Healthy oral mucosa (proteins)	Inhibits
Atrophy/hyperplasia/dysplasia	Promotes
Saliva	
Xerostomia	Promotes
Acidic pH	Promotes
Immunoglobulins	Inhibits
Enzymes	Inhibits
Coliforms	Promotes
Phagocytes	
Immunocompromised	Promotes
Morphogenesis	
Yeast form	Inhibits
Hyphal form	Promotes
Systemic factors	
Altered nutritional states	
Iron/vitamin deficiency	Promotes
Iatrogenic factors	
Therapies	
Antibiotic	Promotes
Corticosteroid	Promotes
Irradiation	Promotes
Smoking	
Cigarette/tobacco	Promotes

References

1. Samaranayake LP. Host factors and oral candidosis. *In:* Samaranayake LP, MacFarlane TW, (eds) Oral Candidosis. London: Wright, 1990; 66-103
2. Bastiaan RJ, Reade PC. The prevalence of *Candida albicans* in the mouths of tobacco smokers with and without oral mucous membrane keratoses. *Oral Surg Oral Med Oral Pathol* 1982; **53**: 148-151
3. Rindum JL, Stenderup A, Holmstrup P. Identification of *Candida albicans* types related to healthy and pathological oral mucosa. *J Oral Pathol Med* 1994; **23**: 406-412
4. Kashima M, Takasahi H, Shimozuma M, Epstein WL, Fukuyama K. Candidacidal activities of proteins partially purified from rat epidermis. *Infect Immun* 1989; **57**: 186-190
5. King RD, Lee JC, Morris AL. Adherence of *Candida albicans* and other *Candida* species to mucosal epithelial cells. *Infect Immun* 1980; **27**: 667-674
6. Marshall KC. *Interfaces in microbial ecology.* Cambridge: Harvard University Press, 1976; 1-11
7. Hazen KC, Glee PM. Hydrophobic cell wall protein glycosylation by the pathogenic fungus *Candida albicans. Can J Microbiol* 1994; **40:** 266-272
8. Bailey A, Wadsworth E, Calderone R. Adherence of *Candida albicans* to human buccal epithelial cells: host-induced protein synthesis and signaling events. *Infect Immun* 1995; **63**: 569-572
9. Cannon RD, Holmes AR, Mason AB, Monk BC. Oral Candida: clearance, colonization, or candidiasis? *J Dent Res* 1995; **74**: 1152-1161
10. Odds FC. *Candida* and Candidosis: A Review and Bibliography, 2nd ed. London: Baillière Tindall, 1988
11. Ollert MW, Calderone RA. A monoclonal antibody that defines a surface antigen on *Candida albicans* hyphae cross-reacts with yeast cell protoplasts. *Infect Immun* 1990; **58**: 625-631
12. Ponton J, Marot-Leblond A, Ezkurra PA, Barturen B, Robert R, Senet JM. Characterization of *Candida albicans* cell wall antigens with monoclonal antibodies. *Infect Immun* 1993; **61**: 4842-4847
13. Kimura LH, Pearsall NN. Relationship between germination of *Candida albicans* and increased adherence to human buccal epithelial cells. *Infect Immun* 1980; **28**: 464-468
14. Samaranayake LP, MacFarlane TW. Factors affecting the *in vitro* adherence of the fungal oral pathogen *Candida albicans* to epithelial cells of human origin. *Arch Oral Biol* 1982; **27**: 869-873
15. Odds FC. *Candida* species and virulence. *ASM News* 1994; **60**: 313-318
16. Santoni G, Gismondi A, Liu JH, Punturieri A, Santoni A, Frati L. *Candida albicans* expresses a fibronectin receptor antigenically related to $\alpha 5\beta 1$ integrin. *Microbiology* 1994; **140**: 2971-2979
17. Knight L, Fletcher J. Growth of *Candida albicans* in saliva: stimulation by glucose associated with antibiotics, corticosteroids and diabetes mellitus. *J Infect Dis* 1971; **123**: 371-377
18. Samaranayake LP, Calman KC, Ferguson MM. The oral carriage of yeasts and coliforms in patients on cytotoxic therapy. *J Oral Pathol* 1984; **13**: 390-393
19. Samaranayake LP, Hughes A, Weetman DA, MacFarlane TW. Growth and acid production of *Candida* species in human saliva supplemented with glucose. *J Oral Pathol* 1986; **15**: 251-254
20. Challacombe SJ. Immunology of oral candidosis. *In:* Samaranayake LP, MacFarlane TW, eds. *Oral candidosis.* London: Butterworth, 1990; 104-123
21. Scully C, El-Kabir M, Samaranayake LP. *Candida* and oral candidosis: a review. *Crit Rev Oral Biol Med* 1990; **5**: 125-157
22. Lamey, P-J, Lamb AB. Prospective study of aetiological factors in burning mouth syndrome. *Br Med J* 1988; **296:** 1243-1246
23. Samaranayake LP, Lamey P-J, Lamb AB, MacFarlane TW. Oral carriage of *Candida* species and coliforms in patients with burning mouth syndrome. *J Oral Pathol* 1989; **18**: 233-235
24. Samaranayake LP, Robertson AG, MacFarlane TW. The effect of chlorhexidine gluconate and benzylamine mouthwashes on mucositis induced by therapeutic irradiation. *Clin Radiol* 1988; 39: 291-294
25. Makrides HC, MacFarlane TW. Effect of commensal bacteria on the adherence of *Candida albicans* to epithelial cells in vitro. *Microbios* 1982; **21:** 55-61
26. Centeno A, Davis CP, Cohen MS, Warren MM. Modulation of *Candida albicans* attachment to human epithelial cells by bacteria and carbohydrates. *Infect Immun* 1983; **39**: 1354-1360
27. Arendorf TM, Walker DM. The prevalence and intra-oral distribution of *Candida albicans* in man. *Arch Oral Biol* 1980; **25**: 1-10
28. Shipman B. Clinical evaluation of oral *Candida* in cancer chemotherapy patients. *J Prosthet Dent* 1979; **41**: 63-67
29. Samaranayake LP, MacFarlane TW. An in vitro study of the adherence of *Candida albicans* to acrylic surfaces. *ArchOral Biol* 1980; 25: 603-609
30. Heimdahl A, Nord CE. Oral yeast infections in immuno-compromised and seriously diseased patients. *Acta Odontol Scand* 1990; **48**: 77-84
31. Diamond RD. Interactions of phagocytic cells with *Candida* and other opportunistic fungi. *Arch Med Res* 1993; **24**: 361-369
32. Greenfield RA. Host defense system interactions with *Candida. J Med Vet Mycol* 1992; **30**: 89-104
33. Kerridge DK. Fungal dimorphism: a sideways look. *In:* Vanden Bossche H, Odds FC, Kerridge D, eds. *Dimorphic fungi in biology and medicine.* New York: Plenum Press, 1993; 3-10
34. Sherwood J, Gow NAR, Gooday GW, Gregory DW, Marshall D. Contact sensing in *Candida albicans*: a possible aid to epithelial penetration. *J Med Vet Mycol* 1992; **30**: 461-469
35. Soll DR. High-frequency switching in *Candida albicans. Clin Microbiol Rev* 1992; **5:** 183-203
36. Warnock DW. Introduction to the management of fungal infection in the compromised patient. *In:* Warnock DW, Richardson MD, eds. *Fungal infection in the compromised patient,* 2nd ed. Chichester: John Wiley, 1991; 23-53
37. Odds FC, Evans EGV, Taylor MAR, Wales JK. Prevalence of pathogenic yeasts and humoral antibodies to *Candida* in diabetic patients. *J Clin Pathol* 1987; **31**: 840-844
38. Tapper-Jones L, Aldred M, Walker DM, Hayes TM. Candidal infections and populations of *Candida albicans* in mouths of diabetics. *J Clin Pathol* 1981; **34**: 706-711
39. Fisher BM, Lamey P-J, Samaranayake LP, MacFarlane TW. Carriage of *Candida* species in the oral cavity in diabetic patients: relationship to glycaemic control. *J Oral Pathol* 1987; 16: 282-284
40. Wilson RM, Reeves WG. Neutrophil phagocytosis and killing in insulin-dependent diabetes. *Clin Exp Immunol* 1986; **63**: 478-484
41. Farman AG, Nutt G. Oral *Candida*, debilitating disease and atrophic lesions of the tongue. *J Biol Buccale* 1976; **4:** 203-226
42. Darwazeh A, Lamey P-J, Samaranayake LP, MacFarlane TW. The relationship between colonisation, secretor status and in vitro adhesion of *Candida* to buccal epithelial cells from diabetics. *J Med Microbiol* 1990; 33: 43-49
43. Coleman DC, Bennett DE, Sullivan DJ, Gallagher PJ, Henman MC, Shanley DB. Oral *Candida* in HIV infection and AIDS: new perspectives/new approaches. *Crit Rev Microbiol* 1993; **19**: 61-82
44. Lal S, Chussid S. Oral *Candidiasis* in paediatric HIV patients. *NY State Dentistry J* 2005; **71**(2): 28-31
45. Coogan M., Fidel PL, Komesu MC, Maeda N, Samaranayake LP. (B1) *Candida* and mycotic infections. *Adv Dent Res* 2006; **19**(1): 130-138
46. Menon T, Umamaheswari K, Kumarasamy N, Solomon S, Thyagarajan SP. Efficacy of flucanazole and itraconazole in the treatment of oral candidiasis in HIV patients. *Acta Trop* 2001; **80**(2): 151-154
47. Costa CR, De Lemos JA, Passos XS, *et al.* Species distribution and antifungal susceptibility profile of oral Candida isolates from HIV-infected patients in the antiretroviral therapy era. *Mycopathologia* 2006; **162**(1): 45-50
48. Wingeter MA, Guilhermetti E, Shinobu CS, Takaki I, Svidzinski TI. Microbiological identification and in vitro sensitivity of *Candida* isolates from the oral cavity of HIV-positive individuals. *Rev Soc Bras Med Trop* 2007; **40**(3): 272-276
49. Woldeamanuel Y, Abate D. Characterization of *Candida albicans* isolates from the oral cavity of HIV-positive patients. *Ethiop Med J* 1998; **36**(4): 235-243
50. Klein RS, Harris CA, Small CB, Moll B, Lesser M, Freedland GH. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Eng J Med* 1984; **311:** 354-358
51. Farmon J, Tavitian A, Rosenthal LE. Focal esophageal candidiasis in acquired immunodeficiency syndrome. *Gastrointest Radiol* 1986; **11**: 213-217
52. Holmstrup P, Samaranayake LP. Acute and AIDS-related oral candidosis. *In:* Samaranayake LP, MacFarlane TW. Eds. *Oral candidosis.* London: Butterworth, 1990; 133-155
53. Hauman CHJ, Thompson IOC, Theunissen F, Wolfaardt P. Oral carriage of *Candida* in healthy and HIV-seropositive persons. *Oral Surg Oral Med Oral Pathol* 1993; **76**: 570-572
54. Hersch EM, Gutterman JU, Mavligit GM. Effect of haematological malignancies and their treatment on host defense factors. *Clin Haematol* 1976; **5**: 425-448
55. Samaranayake LP. Nutritional factors and oral candidosis. *J Oral Pathol* 1986; **15**: 61-65
56. Rennie JS, MacDonald DG. Quantitative histological analysis of the epithelium of the ventral surface of hamster tongue in experimental iron deficiency. *Arch Oral Biol* 1982; **27:** 393-397
57. Joynson DH, Walker DM, Jacobs A. Dolby AE. Defects of cell mediated immunity in patients with iron deficient anaemia. *Lancet* 1972; **2:** 1058-1059
58. Wilton JM, Lehner T. Immunology of Candidiasis. *In*: Nahmias EJ, O'Reilly RJ, eds. *Immunology of Human Infection.* New York: Plenum Medical, 1981; 525-559
59. Rennie JS, MacDonald DG, Dagg JH. Iron and the oral epithelium: A review. *J Royal Soc Med* 1984; **77**: 602-607
60. Cawson RA. Denture sore mouth and angular cheilitis. *Br Dent J* 1963; **15**: 441-449
61. Fletcher J, Mather J, Lewis MJ, Whiting G. Mouth lesions in iron-deficient anaemia: Relationship to *Candida albicans* in saliva and to impairment of lymphocyte transformation. *J Infect Dis* 1975; **131:** 44-48
62. Higgs JM, Wells RS. Chronic mucocutaneous candidosis: associated abnormalities of iron metabolism. *Br J Dermatol* 1972; **86(B)**: 88-102
63. Ferguson MM. Oral mucous membrane markers of internal disease. *In:* Dolby AD, ed. *Oral Mucosa in Health and Disease*, 1st edn. Oxford: Blackwell, 1975; 233-301
64. Dennis M, Itkin IH. Effectiveness and complications of aerosol dexamethasone phosphate in severe asthma. *J Allergy* 1964; **35**: 70-76
65. Stead RJ, Cooke NJ. Adverse effects of inhaled corticosteroids. *Br Med J* 1989; **298**: 403-404
66. Cupps TR, Fauci AS. Corticosteroid-mediated immunoregulation in man. *Immunol Rev* 1982; **65**: 134-155
67. Peterson DE, Sonis TS. *Oral complications of cancer chemotherapy.* The Hague: Martinus Nijhoff Publishers,1983
68. Martin MV, Al-Tikriti V, Bramley P. Yeast flora of the mouth and skin during and after irradiation for oral and laryngeal cancer. *J Med Microbiol* 1981; 14: 457-467
69. Main BE, Calman KC, Ferguson MM, Kaye SB, MacFarlane TW, Mairs RJ, Samaranayake LP, Willox J, Welsh J. The effects of cytotoxic therapy on saliva and oral flora. Oral Surg Oral Med Oral Pathol 1984; 58:545-548