

Alper AKTAŞ¹
Murat ÖZBEK²
Celal TÜMER¹
Ferda TAŞAR¹



REVIEW ARTICLE

XEROSTOMIA IN ELDERLY POPULATION

ABSTRACT

Saliva, which is necessary for oral homeostasis, oral function and maintenance of oral health, is very important for the quality of life. There are various oral complications related to xerostomia. Secretion of saliva and its composition are largely age independent in healthy people. Dry mouth complaint is common in elderly people as a result of a Sjogren's syndrome, radiotherapy, medication use and systemic disorders. Diagnosis of hyposalivation is based on the patient's history and clinical examination. Salivary flow rates can be measured with sialometry. It is very important to elicit an accurate drug and family history. Current treatment approaches for management of xerostomia are directed toward providing relief of symptoms and resulting complications. In order to decide on the most effective way for the treatment of xerostomia in geriatric patients, well organized clinical studies are needed.

Key Words: Xerostomia; Saliva; Etiology; Treatment.



DERLEME

YAŞLI BİREYLERDE AĞIZ KURULUĞU

Öz

Oral hemostaz, fonksiyon ve sağlığın korunması açısından gerekli olan tükürük yaşam kalitesi açısından çok önemlidir. Ağız kuruluğu birçok komplikasyona yol açabilir. Sağlıklı bireylerde tükürüğün salgısı ve birleşimi yaşa bağımlı değildir. Yaşlı bireylerde, Sjögren's Sendrom'u, radyasyon tedavisi, kullanılan ilaçlar ve sistemik rahatsızlıklara bağlı olarak, ağız kuruluğu siktir. Tükürük bezi salgısındaki azalmanın teşhisi hasta anamnezini ve klinik muayeneyi temel alır. Tükürük akışı sialometre ile ölçülebilir. Hastanın ailesel hikayesinin ve ilaç kullanımının tam olarak belirlenmesi önemlidir. Çeşitli nedenler sonucu oluşan ağız kuruluğunun bilinen tedavisi, var olan semptomların ve ortaya çıkan komplikasyonların hafifletilmesini içerir. Günümüzde yaşlı bireylerdeki ağız kuruluğunun daha etkin tedavisine karar verilebilmesi için iyi organize edilmiş klinik çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Ağız kuruluğu; Tükürük; Etiyoloji; Tedavi.

İletişim (Correspondance)

Alper AKTAŞ
Hacettepe Üniversitesi Diş Hekimliği Fakültesi Ağız Diş
Çene Cerrahisi ve Hastalıkları Anabilim Dalı ANKARA
Tlf: 0312 305 22 20
e-posta: rgunaydin@gmail.com

Geliş Tarihi: 23/07/2009
(Received)

Kabul Tarihi: 14/09/2009
(Accepted)

¹ Hacettepe Üniversitesi Diş Hekimliği Fakültesi
Ağız Diş Çene Cerrahisi ve Hastalıkları Anabilim Dalı
ANKARA

² Hacettepe Üniversitesi Diş Hekimliği Fakültesi
Oral Diagnoz ve Radyoloji Anabilim Dalı ANKARA



Saliva, which is necessary for oral homeostasis, oral function and maintenance of oral health (1), has effects on oral lubrication, protection, buffering action, clearance, maintenance of tooth integrity, antimicrobial activities, anti-inflammatory functions, taste, and digestion (2). The average daily flow of saliva is 1 to 1.5 lt. Saliva output is dramatically stimulated by eating: the stimulated salivary flow rate (SSFR) contributes to 80% to 90% of average daily production (3).

Hyposalivation is an objective reduction of saliva secretion, demonstrated using measurements of unstimulated salivary flow rate (USFR) and SSFR (sialometry) (4,5). Dry mouth has multiple oral health consequences and affects the quality of life. The incidence of dry mouth and its public health impact are increasing due to the aging population (1). Dehydration, medication, autoimmune (Sjogren's syndrome) and endocrine (diabetes mellitus) diseases, radiation therapy for head and neck tumors, neuropsychiatric disorders, infections (hepatitis C virus), and several other conditions are common causes of salivary gland disorders (6).

The condition of xerostomia, which comprises a set of symptoms that impact on the individual, can only be assessed by questioning patients (7). Assessing the quality of life, including measures of general health and oral health, such as the Oral Health Impact Profile (OHIP) and the Geriatric Oral Health Assessment Index (GOHAI) can be another way of determining xerostomia (8). Salivary disorders often lead to a sensation of thirst, soreness, mucosa and lip dryness, caries, candidiasis, intolerance to removable dentures, and other oral symptoms. These local symptoms lead to greater risk of dysphagia, choking and aspiration pneumonia, malnutrition, and ultimately, infections and loss of functional ability (9,10).

Salivary function was thought to decline with age, but it is now accepted that the production of saliva and its composition are largely age independent in healthy people (11, 12). Salivary function remains remarkably intact in healthy older persons who are not being treated for medical problems or receiving pharmacological therapy (9). Complaints of a dry mouth (xerostomia) and diminished salivary output (salivary hypofunction) are common in elderly people as a result of a plethora of salivary gland disorders, medication use and medical disorders (13).

Ship and colleagues estimated that approximately 30% of the population 65 years and older experience these disorders (9). Drugs are the most common cause, because most elderly people take at least one medication that adversely affects salivary function (14).

CLINICAL FINDINGS

Hyposalivation contributes to a number of health problems. It can produce serious negative effects on the patient's quality of life by affecting dietary habits, nutritional status, and tooth loss (1). Patients also complain of halitosis, a chronic burning sensation and intolerance of spicy foods (15). Speech and eating difficulties can impair social interactions and may cause some patients to avoid social engagements (9). Xerostomia complaints are mostly encountered at night, owing to the fact that salivary output normally reaches its lowest circadian levels during sleep (16).

DIAGNOSIS

Diagnosis of hyposalivation is based on the patient's history and clinical examination. It is very important to elicit an accurate drug and family history (1). Salivary flow rates can be measured with sialometry. Resting saliva can be collected by asking the patient to dribble into a measuring container for 3–5 minutes, and stimulated saliva can be collected by having the patient chew unflavoured wax or chewing gum base during collection for 3–5 minutes (1).

When examining the effects of pharmaceuticals on the salivary glands, the main point is to draw a distinction between the symptom of dry mouth (xerostomia) and measurable salivary hypofunction. Xerostomia is not a reliable indicator of objectively determined salivary gland hypofunction (7). Saliva flow rate measurements with paraffin wax for 5 to 15 minutes are too long and are inappropriate for older patients with muscular fatigue and impaired or missing teeth (17). Therefore, Matear et al., uses a questionnaire for diagnosis of xerostomia (8). Madinier et al., created a disc method for determining hyposalivation. They record the time until swallowing the disc which is composed of 62.5% white flour, 32.5% sunflower oil, and 5% egg white and baked in 2.8-cm-diameter molds for 20 minutes at 180°C (6).

Early detection of hyposalivation could help to adapt the treatment plan, since it may be easier to suppress xerostomia-associated drugs or to substitute similar types of medications with fewer xerostomic side effects in order to treat oral complications of xerostomia (2,9) (Table 1).

COMMON CAUSES OF HYPOSALIVATION

Some data show age-related changes in salivary constituents, but other evidence shows age-stable production of salivary electrolytes and proteins in the absence of major medical problems and medication use (13). Interestingly, output of

**Table 1**— Various Oral Complications Related to Xerostomia

Dental Caries	Dry Lips	Dry Mouth
Dysgeusia	Dysphagia	Mucositis
Mastication problems	Halitosis	Gingivitis
Candidiasis	Prostheses problems	Sleeping difficulty
Traumatic oral lesions		

the major salivary glands does not undergo clinically significant decrements in healthy older people (18). Other xerostomia induced factors are head and neck radiotherapy, Sjögren's Syndrome and nerve dysfunctions.

MEDICATIONS

The most common cause of salivary disorders is the use of prescribed and non-prescribed medications (13). It has been reported that 80% of the most commonly prescribed medications cause xerostomia and more than 400 medications are associated with salivary gland dysfunctions as an adverse side effect (19). Elderly people take more medications than the rest of the population. The use of medications increases with age; more than 75% of people aged 65 and older take at least one prescription medication (20). Therefore medication induced xerostomia is more common in this group of patients (21).

Common categories of xerostomia related drugs include tricyclic antidepressants, sedatives and tranquilizers; antihistamines; antihypertensives (α - and β -blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors); cytotoxic agents; and anti-Parkinsonism and antiseizure drugs (13). The most common types of medications causing salivary dysfunction have anticholinergic effects via inhibition of acetylcholine binding to muscarinic receptors on the acinar cells. Antidepressant drugs are among the strongest inhibitors of salivation because of their anticholinergic side effects (9). Chemotherapeutic agents have also been associated with salivary disorders (22). After completing chemotherapy, most patients experience a return of salivary function to pre-chemotherapy levels; however, long-term changes in salivary function have also been reported (23).

RADIOTHERAPY

External beam radiation, a commonly used therapy for head and neck cancers causes severe and permanent salivary hypofunction and results in persistent complaints of xerostomia (24). The degree of salivary gland damage depends on the

number of salivary glands exposed to radiation and the dose. The serous acini are considered to be the most radiosensitive cells, followed by mucous acini (25). After the first week of RT, patients will experience viscous saliva, as the serous cell loss will result in diminished water secretion. Eventually, mucous cells are also affected, decreasing the overall volume of saliva produced (26). Dural and Buyukkopru, noted that radiotherapy influences the volume of the saliva, not the concentration of trace elements (27). Radiation doses of 23 and 25 Gy are the threshold, above which permanent salivary gland destruction occurs. After high radiation doses (>60 Gy), degenerative changes progress (1). Intensity-modulated radiotherapy and 3-dimensional treatment planning and dose delivery techniques can minimize radiation exposure of salivary glands, sparing salivary function and improving xerostomia-related quality of life (28). Using pilocarpine during and after radiotherapy can improve symptoms of xerostomia (29, 30).

SJÖGREN'S SYNDROME (SS)

SS is one of the most frequently encountered chronic autoimmune connective-tissue disorders, and it is the most common systemic condition associated with xerostomia and salivary dysfunction (13). SS is more common in females and the prevalence of SS is 1% to 4% in older adults and the nearly 100% in patients with SS (7). Patients with primary SS have salivary and lacrimal gland involvement, with an associated decreased production of saliva and tears. In secondary SS, the disorder occurs with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis and polyarteritis nodosa (7). Swollen major salivary glands are a frequent finding in SS, due to salivary hypofunction, ductal inflammation, and acinar destruction (9). Laboratory tests in SS will frequently be positive for rheumatoid factor (90%), anti-Ro/SSA or anti-La/SSB (50–90%), with the presence of hypergammaglobulinemia (31). Kabasakal et al. carried out a study to determine the prevalence of SS in adult women population and found an incidence of 1.7% for women under 45 years of age, and 6.3% for women over 45 years of age according to the 2002 criteria of the United States-European Consensus Group (32,33). Although advances continue in understanding the etiopathogenesis and management of SS, only symptomatic treatments have been specifically approved. Effective therapy for SS patients requires a multidisciplinary approach including ophthalmologists, dentists, rheumatologists, and other medical experts (9).



OTHER CAUSES OF XEROSTOMIA

Dehydration due to impaired fluid intake, emesis, diarrhea or polyuria can result in hyposalivation. Dry mouth is also a common complaint in patients with diabetes mellitus (19). Psychogenic causes, such as depression, anxiety, stress or fear, can also result in xerostomia. In cases of Alzheimer's disease or stroke, patients may complain of dry mouth in the presence of normal salivary secretion due to altered perception.

MANAGEMENT OF HYPOSALIVATION

Current treatment approaches for management of xerostomia are directed toward providing relief of symptoms and resulting complications (1). According to the severity of symptoms, treatment models include general and local hydration, oral hygiene reinforced with antiseptic mouth rinses, saliva substitutes and lubricants, central (pilocarpine, cevimeline) and local (sugarfree chewing gums and candies) secretagogues, antifungal treatment, topical analgesics before meals, suppression or replacement of causal drugs, dietary modification, and nutritional supplementation (34).

Salivary stimulation is the preferred treatment in patients with residual capacity in the salivary glands. Salivary secretion is increased by nonspecific mechanical and gustatory stimulants. The combination of chewing and taste, as provided by gums and mints, can be effective in relieving symptoms. Sugar-free chewing gums, candies and mints can stimulate salivary output (1,13). Local saliva stimulants have limited effectiveness during the night when especially the symptoms are most severe (1). This is an important disadvantage of local saliva stimulants.

For the treatment of xerostomia and salivary hypofunction by central stimulation, pilocarpine and cevimeline are the most commonly used drugs (35). These drugs are effective in increasing secretions and diminishing xerostomic complaints in patients with sufficient exocrine tissue. Pilocarpine is a nonselective muscarinic agonist, whereas cevimeline reportedly has a higher affinity for M1 and M3 muscarinic receptor subtypes. Cevimeline, enhances salivary secretions while diminishing adverse effects on pulmonary and cardiac function in theory (13). Human interferon-alpha, used as a low-dose lozenge, significantly increases salivary secretion in SS patients (36).

Drug substitutions may help reduce the adverse side effects of medications that produce xerostomia if similar drugs are available that have fewer xerostomic side effects (13). For

example, serotonin-specific reuptake inhibitors have been reported to cause less dry mouth than tricyclic antidepressants (37). Milnacipran, an antidepressive drug and combined noradrenaline-serotonin reuptake inhibitor, provided improved outcomes with less dry mouth symptoms than clomipramine (38). If possible, dividing drug dosages may prevent the side effects caused by a large single dose (13). Taking anticholinergic medications during the daytime, may diminish nocturnal xerostomia, as salivary output is lowest at night (19).

There are various treatment strategies for xerostomia especially secondary to SS. Johansson et al., showed the positive effect of using Salinum with or without chlorhexidine rinses on symptoms of SS (39). There are many studies on acupuncture and xerostomia. Johnstone et al., showed reduced xerostomia in patients resistant for pilocarpine following radiotherapy for head and neck malignancies (40). Chodorowski studied the efficiency of cappuccino coffee treatment for xerostomia in patients taking tricyclic antidepressants and pointed out the improvement in xerostomia. They emphasized that, five minute chewing of 15.0 g of Cappuccino coffee increases the amount of saliva, decreases xerostomia and improves the ability of speech. This effect of coffee lasted from 0.5 to 4 (average about 2) hours (41).

Moreover, several methods such as using primrose oil (42), management with dietary modifications (2) and electro-stimulation of salivary gland (43) were shown to have positive effects on symptoms of xerostomia. Pedersen et al., compared 4 months of daily intake of Longo-Vital (LV), a herbal-based tablet enriched with the recommended daily doses of vitamins, to placebo tablets in terms of their capacities for affecting clinical and laboratory disease parameters in patients with SS. They concluded that LV has a beneficial and prolonged effect on some clinical and immunoinflammatory disease markers in SS (44).

Despite several studies presented in the literature, no ideal treatment exists for radiation-induced salivary dysfunction (45). If saliva secretion cannot be stimulated, symptomatic treatment involves the use of saliva substitutes. Patients should be encouraged to take frequent sips of water throughout the day. Using water during meals can aid in swallowing and improve taste perception. Use of bedside humidifiers, particularly at night, may decrease discomfort due to oral dryness (1).

In conclusion, although oral function may be less affected, xerostomia has a significant and negative impact on the quality of life of elderly individuals (8). In order to decide on the most effective way for the treatment of xerostomia in geriatric patients, well organized clinical studies are required.



REFERENCES

1. Gupta A, Epstein JB, Sroussi H. Hyposalivation in elderly patients. *J Can Dent Assoc* 2006;72(9):841-6.
2. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* 2002;8(3):117-29.
3. Brand HS, Ligtenberg AJ, Bots CP, Nieuw Amerongen AV. Secretion rate and buffer capacity of whole saliva depend on the weight of the mechanical stimulus. *Int J Dent Hyg* 2004;2(3):137-8.
4. Wolowski A, Runte C, Helms S. Oral dryness: Subjective perception and objective causes. *J Am Geriatr Soc* 2003;51(11):1678-9.
5. Navazesh M. Methods for collecting saliva. *Ann N Y Acad Sci* 1993;694:72-7.
6. Madinier I, Starita-Geribaldi M, Berthier F, Pesci-Bardon C, Brocker P. Detection of mild hyposalivation in elderly people based on the chewing time of specifically designed disc tests: Diagnostic accuracy *J Am Geriatr Soc* 2009;57(4):691-6.
7. Fox PC, Busch KA, Baum BJ. Subjective reports of xerostomia and objective measures of salivary gland performance. *J Am Dent Assoc* 1987;115(4):581-4.
8. Matear WD, Locker D, Stephens M, Lawrence HP. Associations between xerostomia and health status indicators in elderly. *J R Soc Promot Health* 2006;126(2):79-85.
9. Ship JA, Pillemer SR, Baum BJ. Xerostomia and the geriatric patient. *J Am Geriatr Soc* 2002;50(3):535-43.
10. Zini A, Sgan-Cohen HD. The effect of oral health on quality of life in an underprivileged homebound and non-homebound elderly population in Jerusalem. *J Am Geriatr Soc* 2008;56(1):99-104.
11. Baum BJ. Evaluation of stimulated parotid saliva flow rate in different age groups. *J Dent Res* 1981;60(7):1292-6.
12. Heft MW, Baum BJ. Unstimulated and stimulated parotid salivary flow rate in individuals of different ages. *J Dent Res* 1984;63(10):1182-5.
13. Turner DM., Ship JA. Dry mouth and its effects on the oral health of elderly people. *JADA* 2007;138(9):15-20.
14. Schein OD, Hochberg MC, Munoz B, Tielsch JM, Bandeen-Roche K, Provost T, and others. Dry eye and dry mouth in the elderly: a population-based assessment. *Arch Intern Med* 1999;159(12):1359-63.
15. Atkinson JC, Wu AJ. Salivary gland dysfunction: causes, symptoms, treatment. *J Am Dent Assoc* 1994;125(4):409-16.
16. Dawes C. Circadian rhythms in the flow rate and composition of unstimulated and stimulated human submandibular saliva. *J Physiol* 1975;244(2):535-48.
17. Ghezzi EM, Lange LA, Ship JA. Determination of variation of stimulated salivary flow rates. *J Dent Res* 2000;79(11):1874-8.
18. Ghezzi EM, Wagner-Lange LA, Schork MA, Metter EJ, Baum BJ, Streckfus CF, Ship JA. Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy women. *J Gerontol A Biol Sci Med Sci* 2000;55(1):M34-M42.
19. Sreebny LM, Schwartz SS. A reference guide to drugs and dry mouth: 2nd edition. *Gerodontology* 1997;14(1):33-47.
20. Chrischilles EA, Foley DJ, Wallace RB, Lemke Jh, Semla TP, Hanlon JT, and others. Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. *J Gerontol* 1992;47(5):M137-44.
21. Thomson WM, Chalmers JM, Spencer AJ, Slade GD. Medication and dry mouth: findings from a cohort study of older people. *J Public Health Dent* 2000;60(1):12-20.
22. Epstein JB, Tsang AH, Warkentin D, Ship JA. The role of salivary function in modulating chemotherapy-induced oropharyngeal mucositis: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94(1):39-44.
23. Meurman JH, Laine P, Lindqvist C, Teerenhovi L, Pyrhonen S. Five-year follow-up study of saliva, mutans streptococci, lactobacilli and yeast counts in lymphoma patients. *Oral Oncol* 1997;33(6):439-43.
24. Shiboski CH, Hodgson TA, Ship JA, Schiodt M. Management of salivary hypofunction during and after radiotherapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;103(S1):S66-73.
25. Stephens LC, King GK, Peters LJ, Ang KK, Schultheiss TE, Jardine JH. Unique radiosensitivity of serous cells in rhesus monkey submandibular glands. *Am J Pathol* 1986;124(3):479-87.
26. Henson BS, Eisbruch A, D'Hondt E, Ship JA. Two-year longitudinal study of parotid salivary flow rates in head and neck cancer patients receiving unilateral neck parotid-sparing radiotherapy treatment. *Oral Oncol* 1999;35(3):234-41.
27. Dural S., Büyükköprü D. [The effect of head and neck radiotherapy on trace elements of saliva.] *Hac Univ Dişhek Fak Derg* 2008;32(1):82-90.
28. Chambers MS, Garden AS, Kies MS, Martin JW. Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. *Head Neck* 2004;26(9):796-807.
29. Zimmerman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. *Int J Rad Oncol Biol Phys* 1997; 37(3): 571-5.
30. Hamlar DD, Schuller DE, Gahbauer RA, et al. Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. *Laryngoscope* 1996;106(8):972-6.
31. Bell M, Askari A, Bookman A, et al. Sjogren's syndrome: A critical review of clinical management. *J Rheumatol* 1999; 26(9):2051-61.
32. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary classification criteria for Sjogren's syndrome. Results of a pros-



- pective concerted action supported by the European Community. *Arthritis Rheum* 1993;36(3):340-7.
33. Kabasakal Y, Kitapcioglu G, Turk T, et al. The prevalence of Sjögren's syndrome in adult women. *Scand J Rheumatol* 2006; 35(5):379-83.
 34. Mouly S, Salom M, Tillet Y, et al. Management of xerostomia in older patients: A randomized controlled trial evaluating the efficacy of a new oral lubricant solution. *Drugs Aging* 2007; 24(11):957-65.
 35. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lochart PB, Tindall E, Suen JY. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial *Arch Intern Med* 2002;162(11):1293-300.
 36. Khurshudian AV. A pilot study to test the efficacy of oral administration of interferon-alpha lozenges to patients with Sjögren's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;95(1):38-44.
 37. Hunter KD, Wilson WS. The effects of antidepressant drugs on salivary flow and content of sodium and potassium ions in human parotid saliva. *Arch Oral Biol* 1995;40(11):983-9.
 38. Leinonen E, Lepola U, Koponen H, Mehtonen OP, Rimón R. Long-term efficacy and safety of milnacipran compared to clomipramine in patients with major depression. *Acta Psychiatr Scand* 1997;96(6):497-504.
 39. Johansson G, Andersson G, Edwardsson S, Björn AL, Manthorpe R, Attström R. Effects of mouthrinses with linseed extract Salinum without/with chlorhexidine on oral conditions in patients with Sjögren's syndrome. A double-blind crossover investigation. *Gerodontology* 2001;18(2):87-94.
 40. Johnstone PA, Peng YP, May BC, Inouye WS, Niemtzw RC. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50(2):353-7.
 41. Chodorowski Z. Cappuccino coffee treatment of xerostomia in patients taking tricyclic antidepressants: preliminary report. *Przegl Lek* 2002;59(4-5):392-3.
 42. Oxholm P, Manthorpe R, Prause JU, Horrobin D. Patients with primary Sjögren's syndrome treated for two months with evening primrose oil. *Scand J Rheumatol* 1986;15(2):103-8.
 43. Erlichman M. Patient selection criteria for electrostimulation of salivary production in the treatment of xerostomia secondary to Sjögren's syndrome. *Health Technol Assess Rep* 1990;8:1-7.
 44. Pedersen A, Gerner N, Palmvang I, Hoier-Madsen M. Longo-Vital in the treatment of Sjögren's syndrome. *Clin Exp Rheumatol* 1999;17:533-8.
 45. Greenspan D. Oral complications of cancer therapies. Management of salivary dysfunction. *NCI Monographs* 1990;9: 159-61.