Dry Mouth
The Malevolent Symptom: A Clinical Guide
1.1 DRY MOUTH: A COMMON WORLDWIDE TORMENTOR

The prevalence of dry mouth

Everyone, at some time in his or her life, suffers from dry mouth: the child who is frightened by Scrooge in the Christmas story; the singer who, for the first time ever, goes on stage to play Tosca; the novice politician who is making his first pitch; the dowager who takes a pill to avoid seasickness. All of them complain of oral dryness. Indeed, the relationship between dry mouth and stress has been known for centuries. In China, dry mouth was used as a sign of guilt until the nineteenth century. Prior to an interrogation, powdered rice was placed into the mouth of an individual suspected of lying. If the rice emerged moist after the questioning, the alleged transgressor was declared innocent. If it was dry, he or she was guilty.

But these forms of desiccation are transitory. They are not our principal concern. The sicca symptoms we concentrate on in this book are chronic and long lasting: weeks, months, years. So, how widespread is this more durable form of dry mouth? The answer to this question depends on who you ask, what you ask and, indeed, if you ask about it. As this section will show, oral dryness is an extremely prevalent condition. But, as observed by Lamb in 1974, it is rarely a primary complaint. Lamb’s observation was reported as a one-liner in Sir David Mason and Dr. Derrick Chisholm’s classic book on saliva in health and disease (Mason and Chisholm 1975). Lamb noted that only 1 in 1,500 patients attending the Glasgow General Hospital listed oral dryness as the main grievance. But when asked whether they suffered from dry mouth, 1 in 10 patients said they did.

The first extensive studies on the prevalence of xerostomia were conducted on elderly Swedes in 1984. A study by Johnson et al. (1984) involved 974 institutionalized individuals; another, by Osterberg et al. (1984), involved 1,148 non-institutionalized adults. The prevalence of oral dryness among the institutionalized subjects was 42%. The rate reported for the non-institutionalized elderly was 16% for the men and 25% for the women. A study involving 529 adults of all ages (18–84 years) was performed 4 years later by Sreebny and Valdini (1989). The subjects in this investigation were randomly recruited from a university-based...
family medicine clinic. The prevalence of dry mouth in these subjects was 29%; 21% for men and 33% for women. In 1989, a marketing survey was conducted involving 18,389 adults (Kanapka 1989). This massive study revealed that 27% of the subjects suffered from dry mouth.

Since the 1980s, many investigations have been performed to assess the occurrence of dry mouth. A liberal sampling of these is shown in Table 1.1.1. These studies, which were conducted throughout the world, revealed that dry mouth is a common condition, but the results of the individual inquiries vary widely. The prevalence of dry mouth ranged from about 13%, in a London family dental clinic, to 63%, in a Finnish hospitalized patient setting. In a sense, this wide range should not be surprising since it comprises peoples of different areas of the world, different ages, different ethnic groups, different environmental conditions and economic levels, males and females, polypharmacy (the intake of many drugs), and underlying disease. Moreover, even the questions asked regarding the presence of oral dryness were different.

You would think that it would be very easy to determine the prevalence of dry mouth. Just ask people if their mouth feels dry and record the answers. C'est ça! But the fact is, it is not easy. If you ask, “Do you have dry mouth?” you get one answer. If you ask, “Does your mouth feel distinctly dry?” you get another answer. If you ask, “Do you suffer from dryness in the morning or evening?” you get a third. And so on. A sample of questions asked is shown in Table 1.1.2.

Scientists are fiercely independent. It is rare for different investigators to use the same question, but this did happen in two studies. In the family medicine clinic study conducted by Sreebny and Valdini (1989), 529 subjects were asked the following question: “Does your mouth usually feel dry?” Almost a decade later, Nederfors et al. (1997), in a much more comprehensive and elegant population-at-large study (n = 3,311), asked the same question. Even though the investigational settings were quite different, the findings were remarkably similar. Twenty-one percent of the males and 33% of the females suffered from oral dryness in the Sreebny and Valdini (1989) study, and 23% of the men and 29% of the women in the Nederfors et al. (1997) investigation.

**Dry mouth: the gender difference**

A significant feature of dry mouth is the fact that it occurs more often in women than in men (Osterberg et al. 1984; Sreebny and Valdini 1989; Locker 1993; Billings et al. 1996; Nederfors et al. 1997). The reason for this is not clear. Hormonal and aging differences have been suggested, but, other than the fact that dry mouth is more prevalent in post-menopausal women, the evidence is meager. Dry mouth is also a prominent feature of many autoimmune diseases. Here too, oral dryness is more commonly seen in women (Table 1.1.3).

**Dry mouth and age**

Many demographic studies have shown that oral dryness is more prevalent in the elderly than in young or middle-aged subjects. In keeping with this is the observation by nurses and other health providers that dry mouth is an extremely common complaint in individuals housed in nursing homes, in long-term care facilities, and in long-stay hospitals. The increased oral dryness is generally associated with an increase in the number of drugs they take and the decline in their overall health. Several cross-sectional studies suggest that the presence of oral desiccation progressively increases with age. Surprisingly, about 15–20% of the 20 and 30-year-olds also complain, when asked, about dry mouth. The frequency is slightly greater in the middle years and it increases to about 30–40% in those over 65.
<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Country</th>
<th>Group/age</th>
<th>n</th>
<th>Dry mouth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. 1984</td>
<td>Sweden</td>
<td>Elderly, institutionalized</td>
<td>154</td>
<td>42%</td>
</tr>
<tr>
<td>Osterberg et al. 1984</td>
<td>Sweden</td>
<td>55, 65, 75 years</td>
<td>973</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male = 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female = 25%</td>
</tr>
<tr>
<td>Sreebny and Valdini 1989</td>
<td>USA</td>
<td>University family practice clinic, 18–84 years</td>
<td>529</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male = 21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female = 33%</td>
</tr>
<tr>
<td>Kanapka 1989</td>
<td>USA</td>
<td>Marketing survey; adults, all ages</td>
<td>18,389</td>
<td>27%</td>
</tr>
<tr>
<td>Gilbert et al. 1993</td>
<td>USA</td>
<td>Elderly residents, 65+ years</td>
<td>600</td>
<td>39%</td>
</tr>
<tr>
<td>Thomson 1993</td>
<td>New Zealand</td>
<td>Institutionalized subjects, 65+ years</td>
<td>359</td>
<td>20%</td>
</tr>
<tr>
<td>Locker 1993</td>
<td>Canada</td>
<td>Ontario residents, 50+ years</td>
<td>907</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male = 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female = 24%</td>
</tr>
<tr>
<td>Narhi 1994</td>
<td>Finland</td>
<td>Elderly inhabitants, 80,85, and 90 years</td>
<td>368</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous dryness = 12%</td>
</tr>
<tr>
<td>Samarannayake et al. 1995</td>
<td>Hong Kong</td>
<td>Elderly residents; long-term care wards</td>
<td>147</td>
<td>35%</td>
</tr>
<tr>
<td>Billings et al. 1996</td>
<td>USA</td>
<td>Population at large</td>
<td>710</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male = 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female = 26%</td>
</tr>
<tr>
<td>Nederfors et al. 1997</td>
<td>Sweden</td>
<td>Swedish inhabitants, 20–80 years</td>
<td>3,311</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male = 23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female = 29%</td>
</tr>
<tr>
<td>Hochberg et al. 1998</td>
<td>USA</td>
<td>Population at large</td>
<td>2,520</td>
<td>17%</td>
</tr>
<tr>
<td>Thomson et al. 1999</td>
<td>Australia</td>
<td>Elderly residents, 60+ years</td>
<td>700</td>
<td>21%</td>
</tr>
<tr>
<td>Field et al. 2001</td>
<td>UK</td>
<td>Adults, family dental practices</td>
<td>1,103</td>
<td>13%</td>
</tr>
<tr>
<td>Pajukoski et al. 2001</td>
<td>Finland</td>
<td>Elderly, hospitalized and outpatients</td>
<td>175 (Hosp)</td>
<td>63% (Hosp)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>252 (OutPt)</td>
<td>57% (OutPt)</td>
</tr>
<tr>
<td>Ikebe et al. 2001</td>
<td>Japan</td>
<td>Elderly, mean age = 66 years</td>
<td>1,003</td>
<td>41%</td>
</tr>
<tr>
<td>Van der Putten et al. 2003</td>
<td>Netherlands</td>
<td>Nursing home; mean age = 78 years</td>
<td>50</td>
<td>52%</td>
</tr>
<tr>
<td>Marchini et al. 2006</td>
<td>Brazil</td>
<td>Institutionalized elderly</td>
<td>553</td>
<td>36%</td>
</tr>
<tr>
<td>Marton et al. 2007</td>
<td>Hungary</td>
<td>Adults, all ages; mean age = 48 years</td>
<td>600</td>
<td>34%</td>
</tr>
</tbody>
</table>
Table 1.1.2. Questions used to assess dry mouth.

<table>
<thead>
<tr>
<th>Question</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your mouth feel distinctly dry?</td>
<td>Osterberg et al. 1984</td>
</tr>
<tr>
<td>Does your mouth feel dry when eating a meal?</td>
<td>Fox et al. 1987</td>
</tr>
<tr>
<td>Do you have dryness of the mouth at any time?</td>
<td>Fure and Zickert 1990</td>
</tr>
<tr>
<td>Do you have mouth dryness?</td>
<td>Osterberg et al. 1992</td>
</tr>
<tr>
<td>Is your mouth sometimes dry?</td>
<td>Gilbert et al. 1993</td>
</tr>
<tr>
<td>During the past 4 weeks, does your mouth feel dry?</td>
<td>Narhi 1994</td>
</tr>
</tbody>
</table>

Table 1.1.3. Dry mouth and gender.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osterberg et al. 1984</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Sreebny and Valdini 1989</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Locker 1993</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Billings et al. 1996</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Nederfors et al. 1997</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

Two wonderful longitudinal, epidemiologic studies were performed to determine the prevalence of xerostomia in, respectively, Canadian elderly people (Locker 1995) and elderly South Australians (Thomson et al. 2006). Locker’s study involved 907 55+-year-old individuals; Thomson et al.’s study was conducted on 60+-year-old subjects. The prevalence of dry mouth at the start of Locker’s study was 15.5%. By the end of the study, 3 years later, it had increased to 29.5%. In Thomson et al.’s investigation (initial n = 1,205), the baseline value for the prevalence of dry mouth was 21.4%. The prevalence increased to 24.8% after 5 years (n = 669) and 11 years (n = 246). These increases support the observations made about the relationship between aging and dry mouth in the cross-sectional studies.

Table 1.1.4. Dry mouth and aging (question asked: Does your mouth usually feel dry?).

<table>
<thead>
<tr>
<th>Age</th>
<th>18–24</th>
<th>25–34</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth (%)</td>
<td>13.3</td>
<td>23.5</td>
<td>23.1</td>
<td>31.8</td>
<td>37.2</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Sreebny and Valdini 1989; n = 529

<table>
<thead>
<tr>
<th>Age</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Dry mouth (%)</td>
<td>17</td>
<td>21</td>
<td>14</td>
<td>21</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

Nederfors et al. 1997; n = 3,311
Table 1.1.5. World estimate of dry mouth populations (millions).

<table>
<thead>
<tr>
<th>Country</th>
<th>Total population</th>
<th>Adult population*</th>
<th>Dry mouth population**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>20.3</td>
<td>15.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Brazil</td>
<td>188.1</td>
<td>141</td>
<td>28.2</td>
</tr>
<tr>
<td>Canada</td>
<td>33.1</td>
<td>24.8</td>
<td>5</td>
</tr>
<tr>
<td>Finland</td>
<td>5.2</td>
<td>3.9</td>
<td>0.78</td>
</tr>
<tr>
<td>France</td>
<td>60</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Germany</td>
<td>83</td>
<td>62.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>7</td>
<td>5.25</td>
<td>1.1</td>
</tr>
<tr>
<td>Hungary</td>
<td>10</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Ireland</td>
<td>4</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Japan</td>
<td>127.4</td>
<td>95.6</td>
<td>19.1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16.6</td>
<td>12.5</td>
<td>2.5</td>
</tr>
<tr>
<td>New Zealand</td>
<td>4.1</td>
<td>3.1</td>
<td>0.62</td>
</tr>
<tr>
<td>Sweden</td>
<td>9</td>
<td>6.75</td>
<td>1.35</td>
</tr>
<tr>
<td>UK</td>
<td>60</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>USA</td>
<td>295</td>
<td>218</td>
<td>44</td>
</tr>
</tbody>
</table>

* 75% of total population.
** 20% of adult population.

Especially interesting in many of the studies is the observation that even young people, when asked, complain of oral desiccation. The reason for it is not known. They, most assuredly, are less affected by disease and consume fewer drugs than the elderly.

Dry mouth: a worldwide tormentor

Percentages generally have no personalities. So what do these numbers really mean in terms of real people? Let us assume that the adult population for any country is about 75% of the total population and that the prevalence of dry mouth is 20% (a very reasonable number). Table 1.1.5 shows an estimate of the numbers of people who may suffer from dry mouth in select countries throughout the world. The data are derived from those countries in which dry mouth studies have been performed. They clearly indicate that millions of people may be affected by oral dryness: in the Americas, 44 million in the United States and 28 million in Brazil; in Europe, 12.5 million in Germany, 9 million in the United Kingdom and France; 2.5 million in the Netherlands; in Asia, 19 million in Japan, 1 million in Hong Kong; and in Australasia, 3 million in Australia and 0.6 million in New Zealand. All over the world, millions! Millions! Although these values are estimates, they strongly imply that dry mouth is a common, widespread, serious health problem.

References

Fox PC, Busch KA, Baum BJ. 1987. Subjective reports of xerostomia and objective measures

Van der Putten GJ, Brand HS, Bots CP, et al. 2003. Prevalence of xerostomia and hyposali-

vation in the nursing home and the relation with number of prescribed medications. Tijdschr Gerontol Geriatr 34:30–36.
1.2 SALIVA: THE REMARKABLE FLUID

Introduction

Saliva is de facto an amazing secretion. A mere glimpse at its variant forms in the animal kingdom attests to its wonders: be it as a drop of venom from animals as diverse as the cobra and the gila monster; be it in the design of the exquisite, silvery threads of the spider’s web; be it in the form of the Chinese bird’s nest soup, which had its humble origins in the salivary laminae of the cave swift; be it as the spaghetti-like tongue of the giant anteater with its sticky ant-bonding saliva; or be it the 150–200 liters of saliva produced by ruminants each day—all affirm the multiple roles of this unique secretion. But these are mere secular examples of its functions. It was Mark (7:33; 8:23) and John (9:1–7) who bore testimony to the sacred value of saliva.

As he was walking along, he observed a man who had been blind from birth. His disciples asked him, “Rabbi, who sinned, this man or his parents, that caused him to be born blind?” Jesus answered, “Neither this man nor his parents sinned. This happened so that the works of God might be revealed in him. I must do the work of the one who sent me while it is day. Night is coming, when no one can work. As long as I am in the world, I am the light of the world.” After saying this, he spit on the ground and made mud with the saliva. Then he spread the mud on the man’s eyes and told him, “Go and wash in the pool of Siloam.” So he went off and washed and came back seeing (John 9:1–7; Fig. 1.2.1).

Besides these divine and mundane roles of saliva, it is generally accepted that the secretions of the salivary glands are of paramount importance for the maintenance of oral health. Among humans, this is based on numerous studies that describe the annoying subjective symptoms and the profound, objective functional losses that occur in persons who lack the ability to produce adequate volumes of saliva. The reduction in the flow induces symptoms that include dry mouth (xerostomia), difficulty with the swallowing of food, and an increased susceptibility to dental caries and opportunistic infections. The latter testifies to the active, protective role that saliva normally plays in the regulation and upkeep of oral health. The oral cavity is characterized by a temperate environment. It has a modestly elevated temperature and a high humidity, and it is regularly supplied with nutriments. These foster the growth of seemingly endless numbers of different aerobic and anaerobic micro-organisms, which, together, form a complex and stable ecosystem.

Saliva plays the key role in the maintenance of the steady state of this system. This becomes particularly evident when the clearance of saliva is blocked. Patients, for example, who are sedated during intensive care may rapidly (often within 2 weeks) demonstrate a shift in their oral microflora from one which is Gram-positive to one which is Gram-negative. This microfloral change may subsequently spread into the respiratory tract, causing morbid pulmonary afflictions. Reduction in the flow of saliva is also intimately associated with the pathogenesis of reflux esophagitis. Moreover, when checking the oral cavity of patients with a dry mouth, food residues are often observed, which are not due to inadequate oral hygiene but to the decreased clearance of the dental and mucosal surfaces by saliva. These are only a few examples of the crucial role that saliva plays in the maintenance of general as well as oral health.

It has been recognized for years that saliva contains many components that, in one way or another, interact with micro-organisms. This regulates and controls the composition of the oral microflora. The main proteins and pep-
tides in human saliva were identified and characterized in the 1970s and 1980s (Fig. 1.2.2). Still, to this day, the precise biological role of many proteins has remained elusive. The translation of their biochemical properties to their biological functions has proved to be difficult and has, sadly, resulted in erroneous and false concepts.

Circa the 1970s, research was focused on the elucidation of the role played by saliva in the protection of dental enamel. This led to the identification of a large number of proteins.
Dry Mouth, The Malevolent Symptom

Components of the immune system also play an important role in saliva’s protective attributes. In particular, more light has been shed on the protective functions of the peptides and other proteins of the immune system and to the mechanisms by which they contribute to the first line of oral defense (Nilsson et al. 1999). In addition, recent research on bacteriostatic glycoproteins reveals that they contain hidden domains that possess microbicidal properties that become available after proteolysis.

Functions of saliva

Saliva is crucial for the maintenance of the health of the oral tissues. In general saliva has three main functions: (1) it protects the mineralized tissues against wear, (2) it whets the oral mucosa, thereby forestalling oral desiccation.
and infection, and (3) it promotes the digestion of food (Fig. 1.2.2). Each of these three general functions can be subdivided into a number of subfunctions. Those involved in the protection of the dental tissues are the inhibition of demineralization and wear and the promotion of remineralization. In addition, a thin salivary film coats the surfaces of the soft and hard tissues of the mouth. This film keeps the tissues moist. Saliva’s ability to defend the oral tissues and thwart infection is subserved by a large number of antifungal, antibacterial, and antiviral systems, as well as by a large number of different proteins present in saliva (Fig. 1.2.2). And finally, saliva plays a crucial role in our daily diet, both in tasting food and in making a bolus to promote the swallowing process. Moreover, it neutralizes acidic constituents and initiates digestion.

A number of salivary constituents are involved in more than one function of saliva. This is particularly true of the mucins; they are essential for nearly all of the functions of saliva. These macromolecules are secreted from virtually all of the seromucous salivary glands. They make the largest contribution to the rheological properties of saliva, such as viscosity, elasticity, and stickiness. The salivary mucins also play a crucial role in wetting and lubricating all oral tissues; therefore in this chapter extensive attention will be paid to the salivary mucins.

### Salivary protein defense systems

Saliva contains a large number of proteins that participate in the protection of the oral tissues. Included among these are lysozyme, lactoferrin, lactoperoxidase, the immunoglobulins, agglutinin, and the mucins. In addition, several peptides with bacteria-killing activity have been identified. These include histatins, defensins, and the only human cathelicidin, LL-37 (Table 1.2.1). Because all of these proteins and peptides have a broad spectrum of antimicrobial activity, there seems to be a considerable overlap in their function. This may account for the observation that susceptibility to oral diseases is not solely related to a single component, but to many (Rudney et al. 1999). Although it appears (Fig. 1.2.2) that there is a redundancy in the defense mechanisms of saliva, this belief is based largely on in vitro studies. In vivo, it is clear that the inhibiting and killing effects of its components are appropriately regulated to maintain homeostasis and that each person develops, maintains, and equilibrates his or her own ecosystem.

In vitro, the antimicrobial activity of the isolated proteins and peptides, for example, histatin, is high; however, in saliva it is not. The reason for the lower activity in saliva is that the antimicrobial activity of histatins is decreased by divalent ions like calcium ions. Such ions are present in saliva in a concentration of about 1 mM. In addition, monovalent ions like sodium ions decrease, though to a lower degree, the antimicrobial activity of histatins. Under healthy conditions non-pathogens are in equilibrium with pathogens; this is not the case in in situ tests.

Since there are so many antimicrobial systems in saliva, they effectuate, under healthy conditions, an ecological equilibrium in the oral cavity. This ecologically balanced system enables saliva to resist the day-to-day attack of the oral cavity by potentially pathogenic micro-organisms.

The oral cavity is the home of numerous different micro-organisms, many of which still await identification and characterization. In addition, an unknown number of micro-organisms reside in the mouth as transient guests. Many of these are potential invaders. To cope with such a wide variety of possible intruders, the oral defense system should be equipped with an armamentarium that is able to cope with and prevent the oral tissues from an uncontrolled colonization by diverse micro-organisms. In this context it has to be noted that the conditions in the oral cavity for some
Table 1.2.1. Examples of antimicrobial proteins in glandular saliva.

<table>
<thead>
<tr>
<th>Salivary (glyco)protein</th>
<th>Tissue of origin</th>
<th>Relative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC5B (Mucin MG1)</td>
<td>All mucous salivary glands</td>
<td>5–20</td>
</tr>
<tr>
<td>MUC7 (Mucin MG2)</td>
<td>All mucous salivary glands</td>
<td>5–20</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>B-lymphocytes: in all salivary glands</td>
<td>5–15</td>
</tr>
<tr>
<td>Proline-rich glycoprotein (PRG)</td>
<td>Parotid</td>
<td>1–10</td>
</tr>
<tr>
<td>Cystatins</td>
<td>Submandibular &gt; sublingual</td>
<td>10</td>
</tr>
<tr>
<td>Histatins</td>
<td>Parotid and submandibular</td>
<td>5</td>
</tr>
<tr>
<td>EP-GP (= GCDFP15, SABP, PIP)</td>
<td>Submandibular, sublingual</td>
<td>1–2</td>
</tr>
<tr>
<td>Agglutinin (= DMBT1, gp340)</td>
<td>Parotid &gt; submandibular &gt; sublingual</td>
<td>1–2</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Sublingual &gt; submandibular, parotid</td>
<td>1–2</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>All salivary glands: mucous &gt; serous</td>
<td>1–2</td>
</tr>
<tr>
<td>Lactoperoxidase</td>
<td>Parotid &gt; submandibular</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cathelicidin (hCAP18, LL37)</td>
<td>Salivary glands, neutrophils</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Defensins</td>
<td>Salivary glands, epithelial cells, neutrophils</td>
<td>&lt;1</td>
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</tbody>
</table>

defense systems are suboptimal. For instance, the microbicidal activity of cationic antimicrobial peptides like defensins, histatins, and LL37 is unfortunately inversely related to the concentrations of salt and divalent ions in saliva. The relatively high concentrations of these compounds in saliva contribute to decreased antimicrobial activity.

Each type of salivary gland secretes a characteristic spectrum of proteins (Table 1.2.1). The complete arsenal of antimicrobial proteins present in whole saliva is thus the sum of the contributions from the different glands. As a consequence, the concentration of a single antimicrobial protein will vary over the day in accordance with the activity of its glandular source. In addition, the functional overlap in the defensive systems means that no single component is necessary for the overall antimicrobial capacity of the salivary defense system. When the function of the parotid glands has been reduced, not only will the volume of saliva be reduced but also its stickiness will increase as a result of the relative increase in the seromucous saliva. Inversely, when the function of the seromucous salivary glands is reduced, this will result in a more watery saliva that does not adhere to the mucosa.

### Protective properties of the major salivary proteins

The most important antimicrobial proteins in saliva, and their glandular sources, are summarized in Table 1.2.1.

#### Immunoglobulins

The salivary immunoglobulins belong primarily (>85%) to the IgA subclass, and to a lesser extent, to the IgG subclass. Together they make up about 5–15% of the total salivary proteins. Salivary IgA is synthesized by B-lymphocytes located in the vicinity of the secretory epithelia. It is secreted into the interstitial fluid, where it is taken up by acinar and ductal cells of the salivary gland and subsequently secreted into saliva. IgG in saliva mainly stems from serum that has leaked into the oral cavity via the crevicular fluid. Because of its high specific binding characteristics, a single immunoglobulin idiotype binds and agglutinates with just one, or at most, a few cross-reactive microbial species. Because of their abundance, the entire population of salivary immunoglobulins binds the majority of the microorganisms present in saliva, thus presenting a broad-spectrum defense system. In contrast to immunoglobul-
Mucins

Mucins are another important class of salivary glycoproteins. In unstimulated whole saliva they are the major component, making up to 20–30% of the total protein. Two types of genetically different salivary mucins can be distinguished (Levine et al. 1987; Loomis et al. 1987): MG1, high-molecular weight mucin (M_r 1–10 MDa), encoded by the MUC5B gene, now designated MUC5B (Thornton et al. 1999), and the low-molecular weight MG2 (M_r ∼130 kDa), the translation product of the MUC7 gene, now designated MUC7 (Bobek et al. 1993).

Characteristic of mucins is the abundance of carbohydrate side chains that are covalently attached to their polypeptide backbones; these force the molecule into an extended conformation (Fig. 1.2.3). On a weight basis, the carbohydrates comprise 60% (for MUC7) to 80% (for MUC5B) of the molecule. The large dimensions and the elongated form of MUC5B, in combination with the presence of a hydrophilic carbohydrate coating, are responsible for the characteristic visco-elastic properties of...
MUC5B-containing solutions (Van der Reijden et al. 1993). MUC5B is synthesized exclusively in the mucous acinar cells of the seromucous salivary glands (Veerman et al. 2003; Nieuw Amerongen et al. 1995). MUC5B is a constituent of the protein layers that form on dental enamel after prolonged incubation with saliva, and is indispensable for the proton-barrier function of these so-called pellicles (Nieuw Amerongen et al. 1987). Because of its hydrophilic properties, MUC5B-containing pellicles lubricate the dental surfaces, protecting them against mechanical wear. Despite its highly diverse population of oligosaccharides, which are potential receptors for bacterial adhesins, MUC5B binds to relatively few oral microorganisms, for example, *Hemophilus parainfluenzae* (Veerman et al. 1995) and *Helicobacter pylori* (Veerman et al. 1997a).

The low-molecular-weight mucin MUC7 differs from MUC5B in structure, localization, and function. MUC7 is a single monomeric protein, decorated with short oligosaccharide side chains that are two or three residues long (Fig. 1.2.4). MUC7 is synthesized in serous acinar and demilune cells of the seromucous

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**Figure 1.2.4.** Schematic models of the high-molecular-weight mucin (MUC5B) and the low-molecular-weight mucin (MUC7). MUC5B consists of polymers and MUC7 of monomers, with short oligosaccharides.
glands (Veerman et al. 1997b, 2003) and is detectable in all seromucous glandular salivas (Bolscher et al. 1999). In contrast to MUC5B, MUC7 binds to a wide variety of bacterial species, including *S. mutans* (Liu et al. 2000). Both mucins have been implicated in protection against viruses (Bergey et al. 1994; Bolscher et al. 2002). Since both mucins are synthesized in all of the seromucous salivary glands, albeit in different cell types, irradiation of the glands will result in the production of an oral fluid with reduced mucins. This will lead to a decrease in the protection of all of the oral tissues and enhance the risk of oral infections.

The study and analysis of salivary mucins is essential for the understanding and properties of an individual’s saliva. They are an enigma and a challenge to researchers.

**Proline-Rich Glycoprotein**

The proline-rich glycoproteins (PRGs) are only present in parotid saliva. They make up about 15–20% of all parotid proteins. PRG is a minor component in unstimulated whole saliva. Upon stimulation its relative concentration can increase to ~10%, due to the increased contribution of fluid from the parotid glands. This cationic glycoprotein (M, 36kDa) interacts particularly with *Fusobacterium nucleatum* and is involved in plaque formation (e.g., Kolenbrander and London 1993). Since PRG is only synthesized in the parotid glands, its concentration in oral fluid is only decreased when these glands have been affected pathologically.

**Protective properties of minor salivary proteins**

Besides the major proteins described above, which account for approximately 50% of the total proteins, saliva contains a number of antimicrobial proteins that are present in lower concentrations (see Table 1.2.1 and Fig. 1.2.2). A number of these are enzymes, which even in low concentration can exert significant biological activity. Examples of antimicrobial proteins with enzymatic activity are lactoperoxidase and lysozyme; examples of non-enzymatic antimicrobial proteins are lactoferrin and agglutinin.

**Lactoperoxidase**

Lactoperoxidase is synthesized and secreted by the salivary glands. A related enzyme, myeloperoxidase, is derived from leucocytes present in the crevicular fluid. The peroxidases inhibit a number of oral and enteric bacteria. Included among these are the lactobacilli, streptococci, actinomyces, and salmonella. Lactoperoxidase catalyzes the oxidation of SCN\(^-\) by hydrogen peroxide, resulting in the formation of OSCN\(^-\). This hypothiocyanite ion can penetrate bacterial cells and oxidize the reduced coenzymes NADPH and NADH. The oxidized coenzymes, in turn, can inactivate glycolytic enzymes like hexokinase. As a consequence, the processes of glycolysis and the production of lactic acid are decreased (Tenovuo and Pruitt 1984; Kussendrager and van Hooijdonk 2000).

Because of its antibacterial attributes, lactoperoxidase has been incorporated into toothpaste. The results of its use are mixed. It appears to have some ability to reduce gingival inflammation (Midda and Cooksey 1986). However, it does not appear to have any significant effect on the flow rate of saliva, on its peroxidase activity, or on dental plaque. Moreover, it does not affect the concentrations of total streptococci, mutans streptococci, lactobacilli, and total anaerobic bacteria (Kirstilä et al. 1994). A recent preliminary study suggests the lactoperoxidase system may reduce breath odor (Shin et al. 2008). It is not known whether a decrease in salivary lactoperoxidase will lead to an enhanced risk of oral infection.

**Lysozyme**

Lysozyme (muramidase) is another example of an antimicrobial enzyme. It is present in saliva,
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tears, sweat, and bronchial mucous. Lysozyme hydrolyzes cell wall polysaccharides, particularly of Gram-positive bacteria, and makes them more vulnerable to lysis. In addition, it may act as an opsonin, thereby enabling white blood cells to phagocytize bacteria, and it may enhance the activity of bacterial autolysins (Laible and Germaine 1985). Remarkably, lysozyme still exhibits bactericidal activity after heat inactivation. This is probably the result of its cationic character. This suggests a two-step working mechanism is involved in the initial enzymatic cleavage of the cell wall. The first step involves an electrostatic interaction of the positively charged lysozyme with negatively charged membrane constituents. This results in an interruption of the membrane organization. It is followed by the killing of the bacterium by the enzymatic activity of lysozyme itself or in combination with other antibacterial systems such as lactoferrin. Studies on the cooperative action of salivary defense systems under physiological conditions are scarce, but it is conceivable that the concerted action of proteins having different mechanisms of action enhance the power of the oral defense. Nothing is known about what happens in the oral cavity when only lysozyme has been decreased.

**Lactoferrin**

Lactoferrin is an example of a non-enzymatic antimicrobial protein. Its antimicrobial action is generally attributed to its iron-chelating property, which deprives micro-organisms of this essential element. In addition, lactoferrin exhibits in vitro anti-inflammatory activities. Several domains are present within its polypeptide chain that exhibit antimicrobial activities. One of these is lactoferricin, an N-terminal peptide of 40 amino acid residues that is liberated following the combined degradation of lactoferrin by pepsin and trypsin. Lactoferricin is a cationic peptide that has a broad spectrum of bactericidal activity (Groenink et al. 1999). In addition, a new antimicrobial domain in lactoferrin has been identified. This has been designated as lactoferrampin; it has 265–284 amino acids (Van der Kraan et al. 2005). Another domain of lactoferrin has been implicated in the binding to salivary agglutinin, suggesting that both salivary proteins can act together. Nothing is known about what happens in the oral cavity if only lactoferrin has been decreased.

**Agglutinin**

Salivary agglutinin was originally characterized as an S. mutans–agglutinating glycoprotein. It was isolated from parotid saliva (Ericson and Rundegren 1983; Lamont et al. 1991; Carlén and Olsson 1995) but is also present in submandibular and sublingual saliva (Ligtenberg et al. 2000; Bikker et al. 2002a). Salivary agglutinin is a member of the Scavenger Receptor Cysteine-Rich (SRCR) superfamily of proteins. It has now become clear that besides S. mutans, a variety of other microbes are bound by agglutinin. The binding appears to be mediated by a stretch of relatively short peptides that are periodically repeated in the agglutinin molecule (Bikker et al. 2002b). It is remarkable that, besides saliva, agglutinins or closely related proteins have been detected in lung fluid, where it is designated as gp-340, and in the brain, where it is designated as DMBT1 (Prakobphol et al. 2000; Ligtenberg et al. 2001). This indicates that the antimicrobial properties of salivary agglutinin are not specific for the oral defense but have a general function in the protection of body tissues. Up to now nothing is known about what happens in the oral cavity if only agglutinin has been decreased.

**Salivary antimicrobial peptides: histatins, defensins, and cathelicidin**

At least three types of antimicrobial peptides (AMPs) can be distinguished in saliva: histatins, defensins, and hCAP18/LL37, a human cathelicidin.
**Histatins**

Of these three antimicrobial salivary peptides, the histatins have attracted the most attention over the last decades. These antimicrobial peptides demonstrate broad antimicrobial activity, not only against bacteria but also against yeasts. They work rapidly and efficiently, are negligibly cytotoxic (Helmerhorst et al. 1999; van’t Hof et al. 2001), and do not evoke resistance. For these reasons such peptides can be used as templates to develop a new generation of antibiotics.

Years before the discovery of the magainins, antifungal peptides found in the skin of frogs, it was reported that histidine-rich proteins in human saliva had killing activity against *Candida albicans* and *S. mutans* (MacKay et al. 1984; Pollock et al. 1984). Since then most of the research on histatins has focused on their fungicidal activity (Edgerton et al. 2000; Gyurko et al. 2001; Helmerhorst et al. 1997, 1999, 2001; Ruissen et al. 2001, 2003; Faber et al. 2003). The histatins are synthesized in the parotid and submandibular glands. They are present in both stimulated and unstimulated saliva. The fungicidal, and to a lesser extent the bactericidal, activity of histatins is sensitive to ionic strength, diminishing with increasing salt concentrations (Helmerhorst et al. 1997). Histatins are, like the majority of the antimicrobial peptides, positively charged peptides. Due to their positive charge they are able to readily interact with the negatively charged bacterial cell walls. In so doing they disrupt and induce pores in the cell membranes (Ruissen et al. 2001, 2003).

As a consequence, leakage occurs of essential cellular constituents, for example, K⁺-ions and ATP. Moreover, the histatins have the ability to enter the cell and destroy some of its essential intracellular structures, such as mitochondria (Helmerhorst et al. 1997, 2001) (Figs. 1.2.5 and 1.2.6). Altogether, these processes result in an instantaneous killing of the microbial and/or fungal cells. Because the histatins are secreted by all of the major salivary glands, no report has been issued focused on the manifestation in the oral cavity in the absence of histatin.

**Defensins**

Defensins are small cysteine-rich cationic proteins that act against bacteria, fungi, and enveloped viruses. The salivary glands contribute relatively little to the concentration of defensins in saliva. Most of them stem from epithelial cells and neutrophils (Mathews et al. 1999). The level of salivary defensin-2 is up-regulated during inflammation (Abiko et al. 2002; Sawaki et al. 2002). A great number of defensins are present in neutrophils, and no data is available

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**Figure 1.2.5.** Microscopic picture of *Candida albicans* (A), incubated during 90 minutes with histatin-5 (B) (Helmerhorst 1999).
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Equilibrium in microbial ecology

The oral cavity is one of the most densely colonized sites of the human body. Its environmental diversity promotes the establishment of different microbial communities, each with their individual characteristic microbial composition. For example, *S. oralis* and *S. sanguis* are abundantly present on the surfaces of the teeth, whereas *S. mutans* forms only a minority of the organisms in the supragingival plaque (MacPherson et al. 1991). Various factors contribute to the establishment of the ecological equilibrium in the oral cavity. Included among these are the diet and the various salivary defense systems. In addition, there is interactive inhibition between the bacterial species. An example of the last mechanism is the discovery of the release of antibiotics by *S. salivarius* that can inhibit the growth of *S. pyogenes* (Upton et al. 2001).

Buffering and remineralizing properties of saliva

The salivary armory contains defensive components/systems that specifically protect the dentition. Both electrolytes, like calcium, and buffering systems are crucial, respectively, for remineralization and acid neutralization. The main buffering system in stimulated saliva is the carbonate/bicarbonate system. In addition, a phosphate buffer is present in saliva that plays a particularly important role in unstimulated and mucous saliva. Because bicarbonate can be resorbed by the ductal cells, its concentration in saliva decreases with decreasing flow rate. Stimulation of the flow rate will thus result in an increase in the bicarbonate concentration with a subsequent increase in the buffer capacity. Salivary bicarbonate, because of its equilibrium with CO$_2$, is able to permanently neutralize acids in the oral cavity. At the same time, specific proteins that are embedded in saliva form a protective coating on the enamel surface. This acts as a barrier and prevents the free diffusion on what takes place in the oral cavity if a defensin is not detectable.

Cathelicidin: hCAP18/LL-37

Like the defensins, hCAP18/LL-37 is derived from both neutrophils and the salivary glands (Murakami et al. 2002; Woo et al. 2003). For hCAP18, the precursor of LL-37, no biological activity thus far has been demonstrated. Activation of hCAP18 results in the release of LL-37, consisting of the C-terminal 37 amino acids, which have broad-spectrum antimicrobial activity (Sørensen et al. 2001). LL-37 is released from its precursor cathelin by proteinase-3. When this proteolytic enzyme is inactive, for example, in the morbus Kostmann, severe periodontitis and recurrent infections have been reported.

Altogether, under xerostomic conditions the antimicrobial systems are severely reduced. This enhances the risk of oral infection.

Figure 1.2.6. Scanning electronmicroscopic picture of *Candida albicans* incubated with histatin-5, showing invaginations in the cell membrane, formation of vacuoles, and disappearance of mitochondria (Ruissen 2002).
of acids. In addition, generic protective systems composed of salivary antimicrobial proteins and peptides provide protection against microbial infections. Secretions from other cells also contribute to the defense of the oral cavity. With the exception of the immunoglobulins, the antimicrobial components in saliva have broad spectral antimicrobial activity. They do not, for example, only eliminate specific (cariogenic) species, like *Streptococcus mutans* (Table 1.2.2). Rather they prevent the massive overgrowth of micro-organisms and govern the establishment and maintenance of a stable ecosystem in which harmless, protective species of bacteria outnumber the potentially dangerous ones. This, per se, is a defensive act. The importance of the establishment of a stable oral flora becomes clear when the oral homeostasis is changed. This may occur due to the intake of immune and inflammatory suppressive medications or broad-acting antibiotics. Within days after taking such drugs, especially in patients who are asymptotic carriers of *C. albicans* (about 50% of the general population), there may be a rapid overgrowth of yeast. It is known that the use of corticosteroids may lead to the rapid onset of candidiasis. Furthermore, the dry mouth condition is known to bear an increased risk of development of oral infections and dental caries. This is due to the fact that the saliva of xerostomic patients has a lower buffer capacity and, as a result, a lower pH. This more acidic environment favors the establishment of select pathogenic micro-organisms, for example, Candida species and *Streptococcus mutans*.

**Moistening and lubrication**

Decreases in the flow of saliva progressively lead to greater and greater complaints of xerostomia. This is particularly evident when the functions of the major salivary glands have been lost, for example, by severe autoimmune diseases or head-neck irradiation. In such cases, the mucosa and epithelia become dry and fragile and are easily damaged and inflamed. Also, rampant decay may ensue. Severe dental caries and all types of dental wear can be observed, caused by both the absence of saliva in combination with a cariogenic diet and the

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<th>Table 1.2.2. Salivary proteins—protective properties.</th>
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<td><strong>Salivary protein</strong></td>
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<tr>
<td>Agglutinin</td>
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<tr>
<td>Cathelicidin (LL37)</td>
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<tr>
<td>Cystatins/VEGh</td>
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<tr>
<td>Defensins</td>
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<tr>
<td>EP-GP</td>
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<td>Histatins</td>
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<td>Immunoglobulins</td>
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<td>Lactoperoxidase</td>
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<td>Lysozyme</td>
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<td>MUC5B (Mucin MG1)</td>
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<td>MUC7 (Mucin MG2)</td>
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<td>Proline-rich glycoprotein (PRG)</td>
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<td>Proline-rich proteins (αPRPs)</td>
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use of acidic (sugar-containing) sweets to stim-
ulate the salivary glands. Furthermore, the
reduction in the flow of saliva leads to a
decrease in the lubrication of the mucosal and
epithelial tissues and a consequent increase in
oral irritation.

**Oral clearance**

One major complaint of patients with a strongly
reduced salivation is the difficulty in making a
bolus of their solid food, like bread. To facilitate
this process they drink more during eating.
Another consequence of the decrease in oral
fluid is that there is a marked decrease in oral
clearance. As a result, food particles remain in
the mouth for a longer period of time and may
be readily observed on the smooth surfaces of
the teeth, between the teeth, and on the oral
mucosal surfaces. This promotes the caries
process.

**Taste acuity**

A number of xerostomia patients complain of a
loss of taste acuity. In others, for example, in
those subjected to head and neck radiotherapy,
the loss may be temporary. However, not all
patients complain. The reason for the ageusia is
not clear. One of the possibilities is that there is
a decrease in the secretion from Von Ebner’s
glands, the small serous glands associated with
the circumvallate taste buds (papillae) of the
tongue. It is known that tastants must be in
solution in order to stimulate the sensory cells
of the taste buds. Another possibility is that
the intracellular signaling processes may be
damaged. In addition, there is some evidence
to show that if the level of zinc is reduced in
saliva, taste may be impaired.

**Future perspectives**

Insights into the mechanisms of action and the
acquisition of new information regarding the
structure-function relationships of antimicro-
bial salivary proteins and peptides will make it
possible to design small, biologically active
peptides that can be used as natural antimicro-
bials. In many cases it is not necessary to bio-
synthesize (by recombinant techniques) the
complete polypeptide chain of biologically
active proteins. It can suffice only to synthesize
the molecule’s functional domain. This opens
new perspectives for the application of pep-
tides as instruments to fight multiresistant
micro-organisms. They may be incorporated as
additives to mouth rinses, inserted into tooth-
pastes, or provided as distinct over-the-counter
products. Such products may restore normal
salivary function to one whose mouth has lost
its natural protection and who suffers from dry
mouth and severe hyposalivation.

**References**

Upregulation of human β-defensin 2 peptide
expression in oral lichen planus, leukoplakia
and candidiasis: an immunohistochemical

Interaction of HIV-1 and human salivary
mucins. J Acquired Immun Def Syndrome
7:995–1002.

2002b. Identification of the bacteria-binding
peptide domain on salivary agglutinin (gp-
340/DMBT1), a member of the scavenger
receptor cysteine-rich superfamily. J Biol

Bikker FJ, Ligtenberg AJM, Van der Wal JE,
et al. 2002a. Immunohistochemical detection
of salivary agglutinin/gp-340 in human
parotid, submandibular, and labial salivary

Bobek LA, Tsai H, Biesbrock AR, Levine MJ.
1993. Molecular cloning, sequence, and speci-
ficity of expression of the gene encoding the
low molecular weight human salivary mucin


Dry Mouth, The Malevolent Symptom


1.3 Living with a Drought: The Patient Speaks

Introduction

“It looks like you suffer from dry mouth,” the doctor said. “Really?” I responded. “Dry mouth?”

The reaction many of us who are dry mouth patients often face is something like, “Is that all? Just a dry mouth? That can’t be too bad.” So, I ask you to imagine, for a moment, life without saliva. Basic life functions that all of us take for granted and enjoy as part of our everyday lives are greatly impacted, leaving the patient devastated by loss, grappling to find ways to cope in a “normal” world, and frustrated by the lack of understanding of how not having enough saliva wreaks havoc with the quality of life. The loss of saliva marks a major life-changing event.

Sjögren’s syndrome

I have Sjögren’s syndrome (SS). It is a disease that takes an average of 7.5 years from the onset of its symptoms to its diagnosis. Dry mouth is one of its numerous symptoms and complications.

I was a lifeguard and taught swimming and sailing as a teenager when I suddenly found myself reacting to the sun with odd rashes and a flu-like feeling. I started avoiding the sun. When my wisdom teeth were removed in my 20s, my parotid glands swelled, giving me the appearance of a chipmunk. The symptom was dismissed by doctors as a “probable, unknown, hard-to-kick infection.”

An incredible fatigue set in that can only be described as “bone-tired” and toxic. I struggled with the long, demanding hours of my job as a television news writer and producer and explained away the fatigue and recurrent parotid swelling as reactions to stress. When my daughter was born 5 years later, I found myself lying in a hospital bed unable to move. I literally could not lift my newborn out of my bed and into the bassinet or back into my bed to nurse. I could not get up to use the bathroom.

I knew something was wrong, but the nurses told me “everyone is tired after having a baby” and that I just needed to make myself move and function. My doctor thought the fever I developed must be due to a pelvic infection, though no evidence existed, and I was prescribed penicillin. In spite of medication, I maintained a low-grade fever throughout the first year of my baby’s life. When I stopped nursing, I developed joint and muscle pain, and that was the key that finally helped unlock a diagnosis for me of primary Sjögren’s syndrome. A visit to a rheumatologist and a lip biopsy at a nearby university health center confirmed the diagnosis.

I soon developed peripheral neuropathy, and, later, other autonomic neuropathies and symptoms that led to questions about potential central nervous system involvement. Vasculitis, purpura, Raynaud’s phenomenon, and antiphospholipid syndrome followed. I and my family live every day with the fear that I will develop non-Hodgkin lymphoma (NHL), a type of cancer that commonly arises in lymphoid tissue present in the salivary glands. My first tentative diagnosis of NHL came in conjunction with my diagnosis of Sjögren’s syndrome, when I was a young mother and alone with my 18-month old child. The lymphoma question raises its ugly head every few years as I develop signs that are frequently associated with its development. When I was pregnant with my second child, I worried about fetal heart block, which can occur when SS mothers are positive for the autoantibody SS-A or RO.

Did I have a dry mouth or dry eyes, the hallmark symptoms of Sjögren’s syndrome? I thought not. Those symptoms came on so insidiously that I did not recognize them until
Chapter 1 The enigma of dry mouth

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and throat. My eyes not only feel gritty, but my eyelids crust and stick together, and I have difficulty focusing. I am sensitive to light and am at risk of corneal ulcers and perforations. My nose is dry, so too my sinuses and skin. A dry vagina makes sex painful and leaves me vulnerable to yeast infections. Even my hair is dry and my nails are brittle and break easily.

I am not alone. There are about four million Americans with Sjögren’s syndrome and many more worldwide. While we share many similar symptoms, we are not all alike, and that makes diagnosis even more complicated. The SS patient’s symptoms do not fit easily into a cloistered diagnostic box and do not necessarily appear in the same order or with the same severity. And besides, we “look just fine,” so how could anything be wrong? Diagnosis is more often an art than a science, especially in the early stages. This is why we as patients need professionals who can ask questions that go beyond their specialty to help link a variety of seemingly disconnected symptoms.

Some friends who have Sjögren’s syndrome have celiac disease, interstitial cystitis, autoimmune thyroid, irritable bowel, autoimmune liver disease, and/or pulmonary fibrosis and frequent pneumonia. About half of us have another major connective tissue disease, such as lupus, rheumatoid arthritis, or scleroderma in addition to SS. We all suffer from side effects of medications such as prednisone. We present a complicated medical picture, and still, we “look just fine.”

Living with a drought

My SS, plus my small children at home, severely limited my “eat out” adventures. But I will never forget the time I attended a family wedding. I arrived hungry and tired after a daylong drive and was delighted to have a plate of wonderful haute cuisine placed in front me—but no beverage. Everyone else at our table

my late 30s. Yet, while I did not recognize symptoms of dryness, I did indeed have reduced tears and saliva. Knowing that dry mouth and dry eye were hallmarks of my disease, I set out to prevent unwanted complications. I entered a clinical trial for dry eye, and a group of ophthalmologists performed a Schirmer test to measure tear flow, rose bengal staining to determine ocular surface damage, and conjunctiva-impression cytology to gauge damage to goblet cells. Even though I did not feel like my eyes were dry, tear production definitely was reduced and I fit criteria for a diagnosis of dry eye.

I requested prescription fluoride and gel trays to prevent cavities associated with Sjögren’s syndrome, but several years later when I broke my leg and was unable to use the fluoride for a couple of weeks, I suddenly developed rampant caries—a sign of reduced salivary flow. I later entered a dry mouth clinical study, where oral health specialists oversaw a second lip biopsy (positive for Sjögren’s syndrome with no change in score compared with the first), the sialometry test to rate salivary flow, scintigraphy to measure salivary gland function, and sialography to examine salivary duct structure. I definitely had reduced salivary flow due to my Sjögren’s, and 2 decades into my disease, I would finally answer the question about whether my mouth and eyes are dry with a resounding yes.

The sequence of appearance of my SS symptoms was not typical. There was, as I have already noted, a multiyear hiatus between the onset of my initial symptoms, especially fatigue, and my recognition of the sensation of oral dryness. Usually dry mouth and dry eyes, either singly or in combination, are the presenting symptoms. Mine were different, but not unique. My experience emphasizes the need for doctors to “think Sjögren’s” even though the patient does not originally complain of oral or ocular desiccation.

Now every part of me that is supposed to be moist is dry. I have severe dry mouth and throat. My eyes not only feel gritty, but my eyelids crust and stick together, and I have difficulty focusing. I am sensitive to light and am at risk of corneal ulcers and perforations. My nose is dry, so too my sinuses and skin. A dry vagina makes sex painful and leaves me vulnerable to yeast infections. Even my hair is dry and my nails are brittle and break easily.

I am not alone. There are about four million Americans with Sjögren’s syndrome and many more worldwide. While we share many similar symptoms, we are not all alike, and that makes diagnosis even more complicated. The SS patient’s symptoms do not fit easily into a cloistered diagnostic box and do not necessarily appear in the same order or with the same severity. And besides, we “look just fine,” so how could anything be wrong? Diagnosis is more often an art than a science, especially in the early stages. This is why we as patients need professionals who can ask questions that go beyond their specialty to help link a variety of seemingly disconnected symptoms.

Some friends who have Sjögren’s syndrome have celiac disease, interstitial cystitis, autoimmune thyroid, irritable bowel, autoimmune liver disease, and/or pulmonary fibrosis and frequent pneumonia. About half of us have another major connective tissue disease, such as lupus, rheumatoid arthritis, or scleroderma in addition to SS. We all suffer from side effects of medications such as prednisone. We present a complicated medical picture, and still, we “look just fine.”

Living with a drought

My SS, plus my small children at home, severely limited my “eat out” adventures. But I will never forget the time I attended a family wedding. I arrived hungry and tired after a daylong drive and was delighted to have a plate of wonderful haute cuisine placed in front me—but no beverage. Everyone else at our table
picked up forks with great relish to partake of the meal—everyone, that is, except for me. I knew I could not take even one bite without liquid, or I would not be able to swallow the food and would choke. I could not join in conversation with those around me, relatives I had not seen in a long time, because my throat was so dry. The beverage did not come until after everyone had finished eating.

When I eat at a restaurant now, I ask for at least two beverages at the start of the meal, because I cannot depend on waiters to refill my water in time to fully enjoy the meal and conversation, but sometimes even that is not enough. I have to be careful to avoid spicy and acidic foods since they irritate my already painful mouth and make me drier. I also shun sugary foods since they exacerbate yeast infections. And so far I consider myself among the more fortunate. Some friends with dry mouth travel with jars of baby food, because they cannot chew, swallow, or digest regular foods.

I suffer from painful oral ulcers, burning mouth, a constant sore throat, chronic hoarseness and cough, bad breath, and chronic oral yeast infections that are almost impossible to conquer. Food often doesn’t taste good because a dry mouth affects one’s ability to taste, and everything tastes like metal. I used to think that eating good food was one of life’s pleasures. When traveling on business, I have faced cracked or broken teeth and the difficulty of finding help for emergency repair, a task that added to the already debilitating fatigue most of us have with Sjögren’s syndrome. I worry that I will have food residue stuck to my teeth, that I will start coughing because of my dry throat, or that I will choke in public. The childhood tale about getting peanut butter stuck to the roof of one’s mouth and not being able to speak comes to mind frequently. We patients seem to have a permanent case of the peanut butter blues.

New airline rules that ban liquids mean that I suffer tremendous discomfort until beverages are available and I can access saliva substitutes or gels. Fortunately, the Sjögren’s Syndrome Foundation has worked with the Transportation Security Administration to ease rules for those with health conditions.

Public speaking, taking walks, and even sleeping soundly become difficult, because I frequently wake up to sip water and then awaken again to run to a bathroom because of all the liquids I have drunk. I spend hours in the dentist’s chair dealing with the repercussions of my dry mouth. If I lose all of my teeth due to dry mouth, I face a future filled with difficult decisions, because dentures do not work well in a parched mouth. I deal with otolaryngology symptoms every day that are related to dryness, including gastrointestinal reflux, indigestion, frequent nosebleeds, sinus problems, and itchy and painful ears.

And now, in my slightly older years, I have become aware that I am a runner. Often, when I eat, my nose runs. When I cry, my nose runs. I’m not sure of the scientific reasons behind this, but I just know that I’m not producing saliva or tears, but my nose, while dry, seems to compensate for this. Perhaps nature finds a way to compensate for our inability to produce adequate saliva and instead results in an even more socially unacceptable and embarrassing symptom.

Lack of knowledge and/or empathy on the part of clinicians affects the way we, as patients, feel with a chronic illness and how well we cope. Patients tell me they were long chastised by their dentists and dental hygienists for not flossing enough or brushing appropriately, because, after all, what else could have caused their rampant caries? Insurance companies tell us that fluoride treatments are for children and not adults, and that people need only to receive regular dental checkups every 6 months instead of the 4-month intervals the Sjögren’s Syndrome Foundation Medical and Scientific Advisory Board recommends. Finally, and in spite of all we go through, a disconnection often occurs.
between clinicians and patients when using the term “dry mouth.”

“Dry Mouth” as a subjective term

When a clinician uses the term “dry mouth” in communicating a diagnosis or in questioning the patient about symptoms, does it have the same meaning for the patient as intended by the clinician? The term “dry mouth” might be scientifically and observationally based for the clinician, but it is a subjective term for the patient. If a clinician asks a patient if he or she has dry mouth, the answer most likely will be “no,” unless the onset is rapid and the degree of severity is so great that the label fits the symptoms and complications or the patient is aware of the term from a medical standpoint. This critical gap in our communication makes a complex diagnosis even more difficult, or we might even say a simple diagnosis more complex.

Often dryness is so insidious and chronic that we as patients adjust to it and come to believe that the feeling of dryness is “normal.” When I asked other Sjögren’s syndrome patients to relay their experiences, Novella from Virginia said, “After taking my history, he (the doctor) asked if my mouth was dry. My quick answer was ‘No.’ He said, ‘Let me show you.’ He took a tongue depressor and laid it on my inner cheek. It stuck. I was stunned. The dryness had come on so slowly that I hadn’t noticed how far from the norm I was.” Another patient said, “My mom was always asking me, ‘Do you need that much butter on your toast?’ I thought I just liked butter, but in hindsight I realized I need my food lubed to slide it down!” A friend with Sjögren’s often has told me that when you live with your dry mouth all the time, you think this is the way your mouth is supposed to feel. We do not use specific terms unless they are explained to us in a way that we can know what they mean.

Describing a dry mouth

What terms do patients use to describe a dry mouth, if they do not call it a dry mouth? I asked Sjögren’s syndrome patients to tell me what words they have used, and many from the Sjögren’s syndrome internet list-serv responded. Words that appear regularly include sticky, burning, stinging, raw, and cotton mouth. Others say their throat feels gunky with saliva that is too thick, their tongue sticks to the roof of their mouth, and their lips stick to their teeth.

Some describe the slow realization that their mouth was indeed dry. Rose Ellen of North Carolina writes, “The first symptom of dry mouth I noticed was a horrible taste that nothing would alleviate. Then I gradually noticed I could not accumulate enough saliva to lick a stamp or an envelope.” Daniel, a Chippewa Indian from Wisconsin, describes his dry mouth as “dry dock, leather tongue, and desert dry,” and Jo Ann from California calls hers the “Velcro throat and mouth.” Erin from Norway says, “I complained daily to my husband that I felt like I was coming down with the flu, because every day I woke up with a horrible sore throat. One day he looked at me seriously and said, ‘You do realize you’ve said that you are coming down with the flu every day for at least 3 months now?’”

Doctors and patients can find clues to a dry mouth through noting changes in our everyday habits. For example, Novella says, “Before I was diagnosed with Sjögren’s, I was feeling miserable. However, I didn’t realize my mouth was dry and didn’t suffer from dental problems. I did notice that eating anything that required a lot of chewing would result in my biting the inside of my cheeks. For this reason I was moving in the direction of soft foods without really knowing the reason why. I also suffered at times from burning tongue. Sometimes I would wake at night with a feeling of being unable to swallow. I learned to keep a glass of water by the bed.” Another dry mouth
patient, Susanne, says she had a range of complaints over time before she was diagnosed. “I began to notice frequent thirst, i.e., a need to wet my mouth; fissures on my tongue; sores in my mouth in a lot of places such as the back of my tongue, the sides of my tongue, the lining of my cheeks, and just below the teeth; a sudden need for fillings when previously regular dental checkups were okay; difficulty swallowing, especially bread or crackers; pain deep in my jaw when chewing; raised areas on the inside of my cheeks where I had been biting them while asleep; and the insides of my cheeks would get caught between my teeth while talking.”

**A life-altering symptom**

Dry mouth affects employment and hobbies. Daniel reports, “I have had jobs where employees are not allowed to have bottled water at their stations and then I end up not being able to talk. I cannot even open my mouth because my tongue is stuck to the roof of my mouth. I have had fits of dry mouth and eyes and gotten stopped by the police. ‘He can’t talk right and his eyes are bloodshot! He’s loaded!’ they said. But I was NOT.” Susan from Utah comments, “I was an academic advisor. I would meet with ten or more students a day and would lose my voice every day.” She finally had to change her job to one that required less speaking. Linda writes, “The dryness has caused social embarrassment. Sometimes food sticks to my teeth. It causes me to slur words or have trouble forming words. I cough and cannot stop until I suck on a candy or something to coat my throat. It’s not predictable, so I never know when it will occur. It happens at work, where I’m frequently on the phone.” And Jo Ann laments, “My singing at church is down to a minimum, and I can’t do long programs.” Singing had brought great joy to Jo Ann throughout her life, and she grieves at her inability to participate.

Dry mouth means spending a lot of time at the dentist’s office and for routine care at home, taking time away from busy schedules, other commitments, and life’s pleasures. Diana comments, “When my mouth goes from very dry to bone dry, I can expect to find one or two fillings loose or a new cavity. Also my bridges do not stay in, and I spend a lot of time at my dentist’s office just getting things re-cemented.”

The dental visit also often means having to push for special attention, and care and required regimens are not easy to accommodate in busy lives. “I have to be extremely vigilant with my oral care or I will suffer cavities, although sometimes they occur anyway,” Linda tells me. “When I go to the dentist I have to make sure I get non-irritating cleaning aids. The dry mouth makes dental work extra difficult, as I can’t keep my mouth open for as long as most people. And I can’t stand to have that spit-sucker attachment hanging in my mouth. I don’t have enough saliva for that! After dental work my mouth will be tender for days.”

Susanne reports that she often comes down with bronchitis after visiting the dentist and especially after undergoing preparations for receiving a crown.

Home regimens are difficult and time-consuming. As Jo Ann reports, “The time I spend in brushing, flossing, fluoride, and everything else I do to maintain tooth integrity makes my pre-Sjögren’s home care look like I was a slacker.”

**Dry mouth affects quality of life**

“My teeth get stuck to the inside of my mouth,” says Lin. “You have to be careful pulling it away, as the tissue inside the mouth is so fragile from the dryness. I cannot swallow food without taking a drink of water. Without water I would choke to death. It’s miserable trying to carry on conversations. There have been times when I just could not talk. My tongue won’t work because it’s so dry.”

Brenda from California notes that eating is no fun, with food remaining “in big blobs” in
her mouth, food becoming tasteless, and finding that she can no longer eat hard-to-chew meat or spicy foods. “Dry mouth has affected my life in ways that have made me become less social,” she says. “Since I cannot taste food as well, I’m reluctant to cook for guests. When I eat out with friends, I have to order something like a soft fish so I won’t choke and cough. Sometimes my voice quits, or I start coughing. It’s easier to stay home.”

Dry mouth is associated with yeast infections (candida) and dry lips. Erin reports, “My lips completely dried out, worse than any chapped lips you could imagine, with pieces of skin coming off, cracking, and bleeding, as well as angular cheilitis. No matter what lip balm I tried it would not go away. I later found out I had candida due to Sjögren’s syndrome.” Brenda says, “Sjögren’s has caused my lips to be constantly inflamed and shredding; it prevents me from wanting to be seen in public.” And Diana writes, “I cannot open my mouth without the corners of my mouth cracking open and leaving me with open sores. My family has nicknamed me ‘Princess Sponge,’ because of my need to constantly drink water.”

And don’t forget the cost

The high financial cost of dry mouth impacts not just the patient but the family as a whole. Susanne writes that she and her family have suffered from the tremendous financial expenses from the dental work she has faced due to dry mouth. Carol says she often had to balance choices between school supplies or extracurricular activities for a child and over-the-counter and prescription medications and doctor appointments.

Dreaming of a better future

The oral health care clinician can be the first professional to put the pieces of the puzzle together and diagnose dry mouth, hyposalivation, and Sjögren’s syndrome. Dentists and dental hygienists also are critical to the ongoing care these patients need. Care depends not only on knowledge but on helpful interactions and relationships with patients. First, doctors and allied health care professionals need to ask the questions that can lead to a diagnosis. Second, an understanding of the impact of such a diagnosis on the patient’s quality of life and communicating that understanding to the patient is important. Both of these points mean developing an ability to listen to the patient. Third, a patient should be made aware of the other specialists he or she should see in order to prevent unnecessary complications and to obtain professional help for those complications that cannot be avoided.

Joan from Maryland comments on her husband’s recent trip to the emergency room for a kidney stone. She says, “One of the medications made his mouth very dry, and he started smacking his lips and complained that his mouth was so dry. I just looked at him and said, ‘Welcome to my world.’ He never complained again.” She humorously suggests one surefire way that clinicians might develop empathy and writes in response to hearing about this text, “I’m glad that the doctors really want to know what it is like to have a dry mouth. I suggest they try atropine or other medication that causes dryness to feel firsthand what it is like. The only problem with that is they know that the dryness is for a limited period of time—not a lifetime.”

An authoritative and excellent resource for both professionals and patients is the Sjögren’s Syndrome Foundation (SSF). The SSF (www.sjogrens.org) strives to increase public and professional awareness of Sjögren’s syndrome; provide support and education for patients, their families, and caretakers; and encourage research. The SSF provides up-to-date information for professionals and patients and has newsletters for each audience, although everyone can benefit from the information in both. Clinicians and researchers can sign up to receive a complimentary subscription to the
publication *Sjögren’s Quarterly*, written for the professional reader to facilitate the exchange of information among clinicians and scientists and report on the latest research, treatment, and management options in Sjögren’s. Professionals also may request complimentary educational brochures for their offices.

By directing your patients to the foundation, you offer them a resource for support and access to educational conferences and materials. The SSF can answer many of their questions and provide practical information and coping strategies that minimize the effects of Sjögren’s syndrome. In addition, the foundation advocates for patients’ needs, tackling such issues as increasing awareness and education; ensuring inclusion in federal Social Security disability guidelines and insurance; obtaining legislative help for over-the-counter costs; and accelerating research.

After all, research is our hope for a better future. Only through research and taking that research from bench to bedside will we find better treatments and a cure. And only through education about dry mouth and diseases that cause dry mouth will we obtain an earlier diagnosis, a better outcome, and better quality life.

**Further reading**


Sjögren’s Syndrome SS-L e-mail list for medical information: www.dry.org./ssl.html.
