CHAPTER 2

Background information
BACKGROUND INFORMATION

In this chapter, additional background information is given on Sjögren’s syndrome and its oral component, in order to provide a solid basis of understanding for the topics dealt with in this thesis. Relevant anatomy and physiology of the salivary glands is presented in the first paragraph for better understanding of the different salivary gland investigations that will be discussed in following chapters. In the next paragraph, an historical overview is given on the syndrome, in order to explain old nomenclature and to place acquired insights into their own perspective. The historical overview is followed by a presentation of current insights on the salivary immunopathology in SS. In the last paragraph, clinical symptoms and signs in SS are presented as observed during the history taking and physical examination. Clinical examination forms the basis for further diagnostic investigations. If experienced in this area, one can skip this chapter and proceed to the next chapters.

ANATOMY AND PHYSIOLOGY OF THE SALIVARY GLANDS

The salivary glands are divided clinically into major and minor salivary glands and functionally into serous, mucous and seromucous salivary glands. The major salivary glands include three pairs of glands, which communicate with the mouth: the parotid-, the submandibular- and the sublingual glands.\textsuperscript{1,2} The parotid gland is the largest of the salivary glands, weighing 14 to 28 grams. This serous gland lies anterior and inferior to the ears. A surgical distinction is often made between the superficial and deep portions of the parotid gland, which are divided by the facial nerve. Anatomically, no capsule or fascia separates these portions. The terminal acini are interconnected with the interlobular ducts through intralobular ducts. Interlobular ducts join to form interlobar ducts. Generally two or three interlobar ducts join at the anterior part of the gland, to form the main parotid duct, named Stensen’s duct. After leaving the gland, the main parotid duct crosses over the masseter muscle. At the anterior border of this muscle, it curves medially, passing through the fat of the cheek and the buccinator muscle. It then runs obliquely in the cheek between the buccinator muscle and the mucosa to terminate at the parotid papilla situated adjacent to the second upper molar. The main duct is about 50 mm long, and has a diameter of 1 to 3 mm with the narrowest part at its orifice.

The submandibular gland is the second largest of the salivary glands. This seromucous gland is located in the upper neck and the floor of the mouth and
wraps around the posterior free margin of the mylohyoid muscle. Its size is about half the size of the parotid gland and it weighs 10 to 15 grams. Submandibular saliva enters the mouth through the main submandibular duct, named Wharton’s duct. The origin of this main duct is similar to the description given of the main parotid duct, with intralobular, interlobular, and interlobar branches. After leaving the hilus of the gland, the submandibular main duct curves around the posterior margin of the mylohyoid muscle and runs forward and upward across the floor of the mouth in the sublingual space. The duct terminates at the submandibular papilla lateral to the frenulum of the tongue. The main duct is about 70 mm long.

The sublingual glands are the smallest of the major salivary glands, weighing 2 to 3 grams. This mucous gland is located beneath the tongue above the mylohyoid muscle. Most often, each sublingual gland drains through several small ducts that open individually into the floor of the mouth, which are named ducts of Rivinus. Sometimes some of the anteriorly located ducts coalesce into a common duct, named Bartholin’s duct. This duct may terminate near the submandibular papilla or may join Wharton’s duct.

The minor salivary glands are usually located submucosally, surrounded by connective tissue, or located between muscle fibres. About 450 to 750 glands are present in the mouth, each weighing less than 10 mg. The serous portion of the
secretion of the minor salivary glands varies per region but generally decreases from the oral to the pharyngeal region, so that the pharyngeal glands are almost purely mucous. The individual glands open directly onto the mucosa. By excreting a steady flow of protective fluid, they play an important role in creating and regulating the local environment.

Gustatory, olfactory, and optic stimuli are known to induce saliva secretion mediated through neural pathways, whereas local muscle activity stimulates saliva secretion mechanically. Oral pain, excitement and anger are also known to induce salivary secretion, whereas emotional stress has a depressive effect. Both sympathetic (predominantly ß-adrenergic) and parasympathetic (cholinergic) stimulation evokes salivary secretion. Salivary secretion totals about 500 to 600 ml per day, though secretion rates may vary considerably between individuals. Fluctuation of secretion during the day is also considerable, being low in the morning, reaching a maximum between noon and 6 PM and declining towards a minimum at night (10 ml/8hrs). The resting, or unstimulated, salivary secretion originates mostly from the submandibular glands, while the parotid glands physiologically respond to stimulation by strongly increasing its relative contribution to the total of saliva secretion. The relative saliva viscosity of the three main salivary glands differs greatly. After stimulation, submandibular saliva has been found to be twice as viscous as parotid saliva, but four times less viscous than sublingual saliva. The viscosity is directly related to the percentage of mucous cells. A decrease of physiological saliva secretion is named hyposalivation, whereas the subjective perception of oral dryness is named xerostomia. These terms, however, are often used improperly as being identical.

**Historical Overview of Sjögren’s Syndrome**

Although the association of dry eyes and dry mouth was described by Hadden in 1888, the coincidence of lacrimal and salivary gland enlargement by Mikulicz in 1888, the systemic nature of ocular dryness by Cougerot in 1925, and the relation between filamentary keratitis and arthritis by Mulock Houwer in 1927, it was not until 1933 that a full description of the condition was given by the Swedish ophthalmologist Henrik Sjögren. Surprisingly, in his own country the value of his thesis was largely underestimated for many years.

Confusion arose regarding the relationship between Sjögren’s syndrome (SS) and the disease reported by Mikulicz. In 1927, Schaffer and Jacobson divided the disease reported by Mikulicz into Mikulicz’s disease, enlargement of the lacrimal
and parotid glands due to lymphocytic infiltration of unknown etiology, and Mikulicz’s syndrome, enlargement of the same glands as a result of systemic disorders such as leukaemia, lymphosarcoma, tuberculosis and sarcoidosis. In 1953, Morgan and Castleman concluded that Mikulicz’s disease, as defined by Schaffer and Jacobson, and SS are identical, sharing the same pathological abnormalities. In the same period Godwin introduced the term ‘benign lymphoepithelial lesion’. It was reported that the histopathological changes of lymphocytic infiltration, acinar atrophy, and cystic or solid duct alterations were seen in both diffusely enlarged salivary glands of patients with xerostomia, as well as in localised salivary gland nodules of patients who were otherwise asymptomatic. As these histopathological changes are identical to the changes seen in SS it was recommended that this condition is regarded as SS if clinical features are present, and as benign lymphoepithelial lesion if no other symptoms are present other than the salivary gland enlargement.

In 1965, Bloch and Buchanan characterised SS as the triad of keratoconjunctivitis sicca (with or without lacrimal gland enlargement), xerostomia (with or without salivary gland enlargement), and a connective tissue disease, most frequently rheumatoid arthritis. The diagnosis of SS requires at least two of the three characteristic features. The presence of a connective tissue disease differentiates between primary and secondary SS. Patients lacking the connective tissue disease but presenting the first two features are said to have primary SS or (formerly) sicca syndrome. This classical triad has been recognised universally and has provided a basis for the more recently developed sets of criteria.

**SALIVARY IMMUNOPATHOLOGY**

Currently, SS is considered to be a disorder of altered immunoregulation in which there is a lymphocyte-mediated destruction of exocrine glands, which in turn leads to diminished or absent glandular secretion and mucosal dryness. Two types of pathological appearance must be considered in the salivary glands in SS: the lymphoepithelial lesion, occurring primarily in the major salivary glands, especially the parotid glands, and focal lymphocytic sialadenitis, occurring in the minor salivary glands.

The lymphoepithelial lesion represents both proliferation of intraparotid lymphoid tissue and infiltration of lymphocytes aggregating around the salivary ducts. The proliferating cells replace the glandular epithelium and may cause clinical enlargement of the gland. With time, metaplastic and hyperplastic ductal epithelium
obliterates the ductal lumen followed by acinar atrophy. These pathological changes may aggravate until the involved salivary gland becomes totally effaced by lymphocytes, leaving only islands of residual deformed ducts, termed epimyoepithelial islands. In 4-5% of the cases, lymphocytic infiltrates may undergo malignant transformation, leading to the development of malignant lymphoma. Due to a close resemblance with MALT-tissue, these lymphomas of the salivary glands have collectively been termed lymphomas of MALT-type. They differ from other lymphomas in that they resemble a chronic inflammatory process and may remain localised for long periods. Their clinical course may be relatively indolent in SS.

The characteristic histopathological feature of minor salivary glands in SS is focal lymphocytic sialadenitis. It consists of a primary lymphocytic infiltrate in glands which appearance is otherwise normal and is characterised by focal aggregates of 50 or more lymphocytes adjacent to normal appearing acini, present in all or most of the glands in the specimen. Various grading systems have been proposed for estimating the relative number of mononuclear cells infiltrating minor salivary gland tissue. The T-cells account for about 80% of the total infiltrate, with the remaining 20% composed of B-cells and plasma cells. It has been suggested that an initial predominance of T-cells is gradually reduced by an accumulation of B-cells and plasma cells. There is a predominance of IgG and IgM bearing plasma cells, reflecting the local chronic inflammatory processes, reducing the number of IgA bearing plasma cells that normally represent at least 70 percent of the plasma cells in the minor salivary glands.

Immunologically, the prevailing abnormality appears to be a polyclonal B-lymphocyte hyperreactivity, directly or indirectly related to alterations in immunoregulatory T-lymphocytes. This B-lymphocyte hyperreactivity is reflected in serum by a polyclonal hyperglobulinemia and the presence of several autoantibodies.

Etiologically, different theories have been proposed over the years. One theory holds a genetic abnormality of the immune system responsible. This may involve an abnormality of the B-lymphocytes in which there is spontaneous B-lymphocyte activation, or possibly an abnormality of the T-lymphocytes in which excessive T-helper function or decreased T-suppressor function permits or induces B-lymphocyte over-activation and production of antibodies. Another possibility is that the disorder results from an antigenic challenge. The acquired antigenic stimulus may be a viral disease that alters surface autoantigens, which in turn stimulates B-lymphocyte activation and the production of autoantibodies. A third possibility is a combination of the two aforementioned theories, in which there is an interaction of
an acquired exogenous stimulus with a certain genetic susceptibility. Furthermore, abnormal apoptosis, and interaction of sex steroid hormones have been proposed to induce initial autoimmune responses.

**ORAL EXAMINATION**

In the full expression of SS, oral and ocular symptoms and signs predominate, but due to its diffuse exocrinopathic involvement, several or all exocrine gland systems may be involved. Dryness from exocrine gland dysfunction is, therefore, certainly not limited to the eyes and the mouth, but may extend to all mucosa-covered surfaces in the body, e.g. in the vagina, nasal cavity, oesophagus, pharynx, vocal cords, airways and lungs. In addition to mucosal dryness, skin dryness is also common. Symptoms in SS are not restricted to dryness, as the systemic autoimmune character of the syndrome often induces general complaints; most patients suffer from chronic fatigue, whereas frequently arthralgia and myalgia are experienced as well. Internal organs such as the kidneys, the lungs, the bladder, and even the cerebrum may also be involved in SS.

Oral symptoms in SS may consist of sensation of oral dryness, impaired speech, eating difficulties, pain and swelling. It is not known how much saliva is necessary for allowing normal oral function, for oral comfort, and for the maintenance of oral health. The symptoms occur either alone or in combination. Oral dryness in SS results from the lack of saliva that normally moistens the mouth and lubricates the oral mucosa. Often, the first complaints of oral dryness arise at night due to decreased resting salivary secretion rate. With time, oral dryness is also perceived during daytime due to a decrease of both resting as well as stimulated salivary secretion rate. Predilection sites for the sensation of oral dryness are the anterior part of the palate and the dorsum of the tongue, due to a relatively low number of submucosal minor salivary glands present in these areas. The speech difficulties might relate either to impaired tongue movement in a dry and sticky mouth, as well as to hoarseness from dry and irritated vocal cords in case of generalised mucosal dryness. Eating difficulties may include impaired taste due to a lack of saliva (necessary to dissolve food components) and to atrophy of the tongue epithelium. The impaired taste is usually limited to decreased taste acuity and rarely presents as a complete loss of taste as temporarily may occur after radiotherapy. Eating difficulties may also include masticatory problems due to a sticky and painful oral cavity, poor dentition or functional denture-problems, and swallowing difficulties.
Impaired swallowing may either relate to problems with food bolus formation and translocation and mucosal lubrication (oesophageal dryness) as well as to oesophageal motility disorders.\textsuperscript{60,61} Oral pain may either result from hypersensitivity of the oral mucosa, dental caries, opportunistic mucosal infection, or (acute) sialadenitis. Hypersensitivity of the oral mucosa occurs quite frequently in SS patients as a result of inadequate moistening of the mouth. This renders the mucous membranes more vulnerable to mechanical trauma and to chemical irritants from food and beverage. Depending on its progression, dental caries causes pain that varies from mild and localised pain reactions to cold or heat to unbearable pulsating pain at one site of the mouth. Opportunistic mucosal infections usually present with a mild pain if painful at all, whereas acute sialadenitis can be very painful, accompanied with symptoms of malaise and feeling ill. Several aspects of the symptoms may be especially informative, such as their duration, whether they are chronic or recurrent and whether they relate to predisposing factors. Furthermore, information about the general health and medical history of the patients has to be obtained. The patient should explicitly be asked about previous surgery or radiotherapy in the head and neck region. Drug intake should also be noted as many drugs may suppress salivary gland function.\textsuperscript{62} Examples of commonly prescribed xerogenic drugs are antihistaminics, antihypertensives and psychotropic drugs.

Examination of the salivary glands includes meticulous inspection of the head and neck area as well as intraoral inspection. Obviously, swelling in the area of the major salivary glands must be noted. The appearance of the oral mucosa, especially on the tongue, may reveal salivary gland dysfunction. It should be determined whether or not physiological pooling of saliva is present sublingually. The dental status and oral hygiene must be noted. The orifices of Stensen’s and Wharton’s duct must be carefully inspected. Palpation provides information on the size, consistency and tenderness of the salivary glands and any associated masses. A unilateral or bilateral parotid or other salivary gland swelling occurs frequently, either recurrent or chronic. Tear gland swelling is uncommon. Other exocrine glands are targeted as well, though their involvement is clinically less visible due to their localisation and their small size. Chronic swelling of salivary glands, especially if profound, may indicate the presence of a malignant lymphoma. The head and neck region must therefore also be examined for presence of enlarged lymph nodes. External pressure on the salivary glands may provoke an increased flow of saliva that should be inspected for signs of inflammation. In cases of gross ductectasis in the parotid gland, a spurt of
saliva will be seen. In contrast, a sudden release of saliva during massage of the submandibular gland is normal. If possible, palpation should be done bimanual. Size and consistency of the glands and their main excretory ducts can be optimally assessed by inserting two fingers intraorally while the other hand provides gentle support from outside the mouth.

The intraoral symptoms and signs of SS are not specific, being shared with other conditions in which salivary gland function is diminished. The superficial location of the salivary glands, however, easily permits inspection and palpation. A detailed history together with a thorough examination provides valuable information for a differential diagnosis. It may further reveal problems secondary to salivary gland dysfunction, which need treatment. Subsequently, additional diagnostic procedures, as described in the next chapters, can be performed in order to differentiate between SS and other conditions with similar symptoms and signs.

REFERENCES