Sjögren's syndrome

information for patients and professionals

Joop P van de Merwe

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with the following chapters:

Sjögren's syndrome: an overview

1

Sjögren's syndrome is characterized by eye and mouth symptoms caused by an abnormal composition and/or impaired production of tear fluid and saliva.

Inflammation occurs in the lacrimal and salivary glands (figures 1.1 and 1.2) and this means that there is an accumulation of cells (lymphocytes in this instance) in these glands.[1-3] In addition to the eye and mouth complaints, almost all patients are also affected by general symptoms. These are not characteristic of Sjögren's syndrome because they are also frequently found in other autoimmune diseases. Examples include pain or inflammation of the joints, fatigue and Raynaud phenomenon.

Sjögren's syndrome is a generalized autoimmune disease. The term *autoimmune disease* means that the disease is caused by the immune system, the body's defence mechanism; *generalized* indicates that more than one organ is involved in the disease.

Abnormalities in the composition and quantity of tear fluid and saliva may also be due to causes other than Sjögren's syndrome. One important cause is medication (see tables 1.1 and 1.2 and chapter 14). Inflammation of the lacrimal and salivary glands can likewise have other causes.

The most common symptoms

The most common symptoms of Sjögren's syndrome are eye irritation, dry mouth, fatigue, joint pain, muscle pain and Raynaud phenomenon.

Table 1.1 A few causes of dry eyes

- medication
- diseases (including Sjögren's syndrome, sarcoidosis, diabetes mellitus, Parkinson's disease, AIDS)
- vitamin A deficiency
- eyelid abnormalities and/or non-closing eyelids
- dry environment

Eye symptoms

Characteristic eye symptoms are *burning* eyes and a *gritty feeling* as though there is sand or a foreign body in the eyes. Patients do not usually complain that their eyes feel dry! In addition, the white of the eye may look rather red and the eyes may sometimes be glued up first thing in the morning, suggesting *blepharitis* (see elsewhere). Symptoms increase when reading, looking at a screen (*e.g.* television or computer) or on contact with cigarette smoke.

In order to be able to see clearly, it may be necessary to blink a few times to refresh the tear film. The lacrimal glands may be swollen in some Sjögren's patients.

Mouth symptoms

The most characteristic symptom of the mouth is that patients need to drink when eating dry food in order

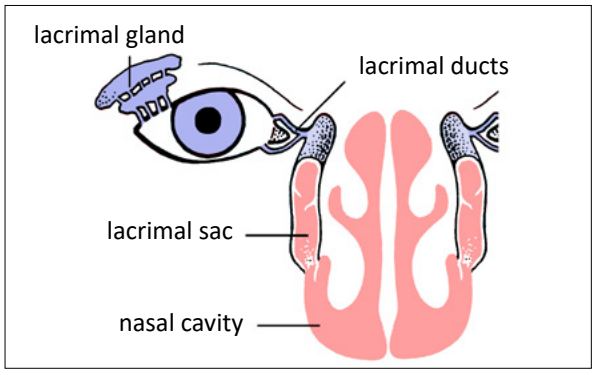

Figure 1.1 *The lacrimal gland, lacrimal ducts, lacrimal sac and the duct to the nasal cavity.*

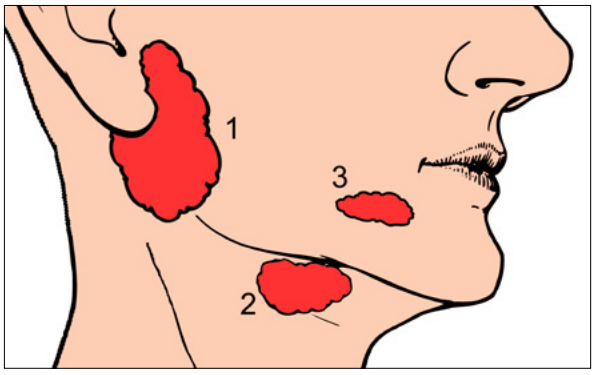

Figure 1.2 *The major salivary glands: 1. parotid gland 2. submandibular gland 3. sublingual gland.*

Table 1.2 A few causes of a dry mouth

- medication (including antihypertensives, antidepressives, sleeping drugs, diuretics, antihistamines)
- diseases (including diabetes mellitus, Parkinson's, AIDS)
- radiation
- chemotherapy
- nerve damage (facial paresis)
- various (including anxiety, dehydration, breathing through the mouth)

to be able to swallow it (this is known as the *cracker sign*). The dry mouth often makes talking difficult and the patient may have a sore throat. There may also be the feeling of having an obstruction in the throat that cannot be swallowed. At night the Sjögren's patient will often have a glass of water next to the bed.

The poor quality of the saliva may be the cause of severe dental decay around the gum line.

A burning mouth and tongue, with cracks in the corners of the mouth (figure 1.3 left) is suggestive of a *Candida albicans* yeast infection. This may be difficult to identify since it is a so-called erythematous candidiasis, mainly with red mucosa and without a white coating.[4] A yeast infection can also be the cause of a so-called black hairy tongue (see figure 1.3 right).

Swelling of the salivary glands is seen in approximately 20% of Sjögren's patients, often episodic or occurring on one side of the face. Figure 1.4 shows one patient with bilateral swelling and one with swelling on only one side.

Thirst is not the same as a dry mouth. Thirst does not form part of Sjögren's syndrome but may be an indication of diabetes mellitus.

Fatigue

For many Sjögren's patients, fatigue is the worst complaint and may be invalidating.[5-12] It often varies with good and bad days and may sometimes increase very suddenly. Although the fatigue may be present right from the moment of getting up in the morning, it usually increases during the course of the day and improves after a rest. Fatigue is discussed in detail in chapter 6.

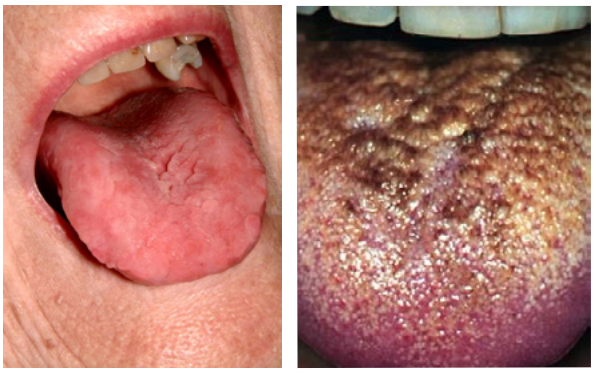

Figure 1.3 *Dry tongue. Cracks in the corner of the mouth often indicate a Candida albicans yeast infection. A yeast infection may also be the cause of a so-called black hairy tongue (photo right)*

Muscle and joint pain

Muscle and joint pain often occurs in Sjögren's syndrome and usually varies in severity and the site of the pain. Inflammation (*arthritis*) is present if the joints are swollen, hot or red. Joint inflammation usually occurs symmetrically (in other words both left and right) and is more likely to affect the small joints of the hands and feet rather than large joints such as knees or ankles. It usually subsides of its own accord within a few weeks and causes no damage to the joints as in the case of rheumatoid arthritis.

Raynaud phenomenon

With Raynaud phenomenon[13-16] the hands and feet turn bluish-white in the cold (figure 1.5). This may

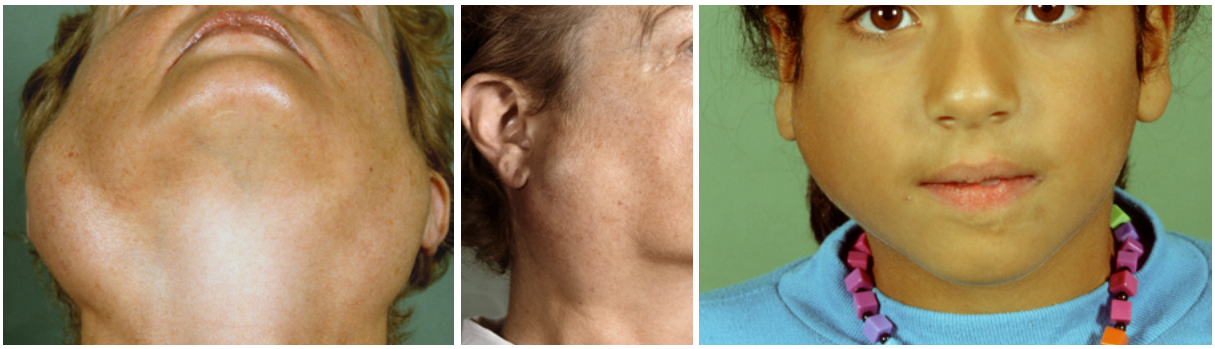

Figure 1.4 *Swelling of the parotid glands in Sjögren's syndrome. Left: bilateral swelling; middle: the same patient as on the left photo; right: mainly unilateral swelling.*

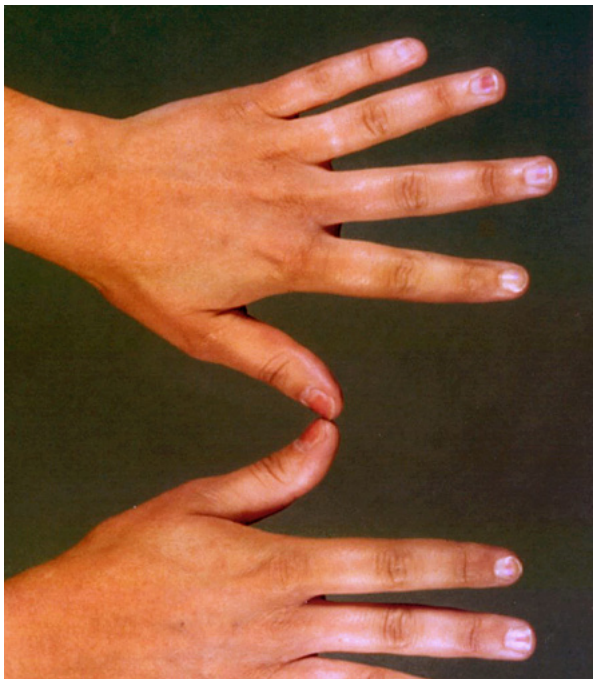

Figure 1.5 *Raynaud phenomenon. Note the blanching of the phalanges.*

even occur sometimes at room temperature or under the shower. The hands may be painful and stiff. This phenomenon may be limited to the fingers (toes), the whole hand (foot) or extend as far as the wrist (ankle).

The blanching is caused by impaired blood flow (*ischaemia*) as a result of constriction of the blood vessels. The bluish discoloration occurs when there is an inadequate supply of oxygen to the tissue (*cyanosis*). Once the hands and feet warm up, they may turn red as the blood vessels dilate (*hyperaemia*). Fissures may occur on the fingertips and take a long time to heal. Raynaud phenomenon may occur years before Sjögren's syndrome or another autoimmune disease manifests itself.

How do you get the disease?

Sjögren's syndrome is considered to be an auto immune disease, a condition caused by the immune system.[17] It is unknown why the immune system does this. There are as yet no indications that it could be a response to a viral or bacterial infection, to specific lifestyles, to food or any other environmental factors. The only known factors that increase the risk of developing the disease are: being female, having blood relatives with the disease (*e.g.* mother, aunt or sister) and having another related autoimmune disease. In addition certain HLA antigens (genes that are best known for the important role they play in tissue transplantation) have a slight influence on this risk (see chapters 3 and 15).

How is Sjögren's syndrome diagnosed?

The diagnosis is made on the basis of criteria. Criteria are agreements relating to the signs and symptoms a patient must have for a diagnosis to be made. These criteria are in the first instance intended to be used for the purpose of scientific research into the disease. In the past many different sets of criteria have been drawn up for Sjögren's syndrome.[3] At the present time the so-called American-European criteria are most commonly used (see chapter 4). [18-21] A major problem is that these criteria only detect a minority of patients with the disease (see also the chapter on incomplete Sjögren's syndrome.

Can the disease be treated?

People often hear that there is no treatment for Sjögren's syndrome. This is not correct. What is true, however, is that the underlying cause of Sjögren's syndrome cannot be removed. But in this respect Sjögren's syndrome does not differ from other diseases such as rheumatoid arthritis or systemic lupus erythematosus.

Despite the fact that there is no treatment that will actually cure the disease for good, treatment can improve the signs and symptoms in many patients. In addition, it is possible to prevent complications from the disease in some of the patients. Treatment is discussed in chapter 5.

What can I expect?

The course of the disease differs per person. The signs and symptoms often appear to go in waves, without any clearly identifiable reason. The most severe symptom is often fatigue, followed by eye irritation and dry mouth. In general terms, changes mainly occur in the first 5 years of the disease, followed by a stable course in the majority of patients (see also chapter 19).

After a time some patients have little bother from the disease and can successfully cope with it, with a few adjustments. Others, however, feel that their life is totally wrecked by their illness. A large number of the patients with Sjögren's syndrome lie somewhere between these two extremes.

Since the disease is not usually life-threatening, life expectancy is more or less normal. However, the fatigue, eye irritation and mouth problems have a very negative impact on the quality of life. These consequences of the disease are often underestimated.

Nevertheless, serious complications may sometimes occur. These include the (malignant) non-Hodgkin's lymphoma (in 5% of patients),[1,26-32] a specific type of inflammation in the lungs (lymphocytic interstitial pneumonitis) and a specific form of inflammation in

Table 1.3 Prevalence a of Sjögren's syndrome

source	*population studied*	*diagnostic criteria used*	*prevalence (%)*
Jacobsson *et al* 1989 [33]	population Malmö 52-72 yrs	Copenhagen [41]	2.7
Bjerrum 1997 [25]	persons 30-60 yr	Copenhagen [41] preliminary European [18]	0.2-0.8 0.6-2.1
Dafni *et al* 1997 [22]	women from 18 yr in closed rural community in Greece	validated European [20]	0.6
Thomas *et al* 1998 [23]	general practice population south Manchester - 18-75 yrs - > 54 yr	preliminary European [18] *idem*	3.3 4.6
Tomsic *et al* 1999 [24]	adults Slovenian population	validated European [20]	0.6
Bowman *et al* 2004 [34]	Caucasian women GP lists in Birmingham		0.1-0.6
Trontzas *et al* 2005 [35]	adult white population in Greece *idem*, female population	American-European [21]	0.15 0.29
Sánchez-Guerrero *et al* 2005 [36]	ambulatory patients attending a tertiary care centre in Mexico	American-European [21]	>13.3
Alamanos 2006 *et al* [37]	referral adult population north-west Greece	American-European [21]	0.093
Kabasakal 2006 *et al* [38]	adult women in Turkey	preliminary European [18] American-European [21]	1.56 0.72
Haugen *et al* 2008 [39]	population Norway aged 40-44 yr population Norway aged 71-74 yr	preliminary European [18] validated European [20] preliminary European [18] validated European [20]	0.44 0.22 3.39 1.40
Birlik *et al* 2008 [40]	general Turkish population	preliminary European [18] American-European [21]	0.28 0.16

prevalence: % persons in the population with the disease

Why is it called Sjögren's syndrome?

A syndrome is "a set of symptoms which occur together; the sum of signs of any morbid state; a symptom complex. In genetics, a pattern of multiple malformations thought to be pathogenetically related" according to Dorland's, the medical dictionary used by generations of doctors (*Dorland 28th edition © 1994 W.B. Saunders Company).* In practice, however, the term syndrome is only applied to symptoms when the reason why these symptoms occur in combination is unclear.

In 1933, Henrik Sjögren (fig. 1.6) was the first to describe the combination of *keratoconjunctivitis sicca* (KCS, "dry eyes") and dry mouth with inflammation of joints (*rheumatoid arthritis*). It was precisely the occurrence of arthritis in patients with KCS and a dry mouth that was so new (see also chapter 20, answer 16). The term syndrome was therefore the obvious one to apply since the relationship between the eye and mouth symptoms on the one hand and the arthritis on the other was by no means clear.

This relationship is still unclear today but the definition of Sjögren's syndrome has changed. It is now defined as the combination of specific eye and mouth symptoms with objectively determined abnormalities in the (function of the) lacrimal and salivary glands; (rheumatoid) arthritis is no longer an essential element.

However, the combination of signs and symptoms caused by impaired functioning of the lacrimal and salivary glands is much easier to understand, particularly in relation to new insights into the role of muscarinic M3 receptors (see chapter 3). Since arthritis no longer forms part of the definition of Sjögren's syndrome, it is no longer really logical to use the word syndrome. The term Sjögren's disease would in fact be a more appropriate description nowadays.

For historic reasons the name Sjögren's syndrome will continue to be used for the time being despite it has become clear now that cases were described independently by von Mikulicz-Radecki from Poland (fig. 1.7), W.B. Hadden (England), Hutchinson (England) and Fischer (Germany), all in 1888, eleven years before Henrik Sjögren was born. Similar cases were also described by H. Gougerot (1881-1955) in 1925 (dermatologist from France) and A.W. Mulock Houwer (1884-1983) in 1927 (opthalmologist from the Netherlands).

So, both words in the name Sjögren's syndrome are not correct.

Figure 1.6 *Henrik Sjögren (1899-1986), the Swedish ophthalmologist whose name was given to the syndrome.*

Figure 1.7 *Johannes von Mikulicz-Radecki (1850-1905), the Polish surgeon who described bilateral parotid and lacrimal gland enlargement in 1888.*

Prevalence

About 1 out of 250 women between 40-44 years and 1 out of 30 between 71-74 years of age will have Sjögren's syndrome. For men, these numbers are 10 times lower (see text).

the kidneys (glomerulonephritis or inflammation of the kidney filter system).

How common is the disease?

How commonly a disease occurs (*prevalence*) depends on the criteria used for the diagnosis and the composition (male/female; age distribution) of the population being studied. Table 1.3 shows studies that used the Copenhagen [41] or various versions of the European criteria including the most recent American-European criteria.[18-21] The studies show very different prevalence rates. Recent studies that used the American-European criteria show lower prevalences than earlier studies. As can be expected for a chronic disease with normal life expectancy, the prevalence increases with age.

It is generally agreed that diagnostic criteria do not detect all persons with the disease, due to the high specificity that is required for the use of the criteria for scientific studies (see chapters 4 and 19). Diagnostic criteria for various diseases usually detect about half of the patients that experts consider to have the disease in question. In my opinion, the most reliable prevalence numbers are those from Haugen *et al* (2008) [39] using the validated European criteria (table 1.3). The real prevalence numbers are probably twice as high (see above). This would mean that the prevalance is 0.4 for people between 40-44 yr (4 per 1000) and 2.8 for people between 71-74 yr (28 per 1000). As Sjögren's syndrome affects women about 9x more frequently than men, it can be calculated that about 1 out of 300 women between 40-44 years and 1 out of 40 between 71-74 years of age will have Sjögren's syndrome.

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Salivary glands and saliva

Saliva has many functions in the mouth such as
- protection of the teeth and mucous membranes
- lubrication
- when eating (taste, digestion)
- protection against infection

The mouth has three types of major salivary gland (see figure 1.2):
- the parotid gland
- the submandibular gland
- the sublingual gland

There are also numerous minor salivary glands in the lip, palate and cheeks. Each type of gland produces saliva of a specific composition. The parotid gland makes watery saliva containing various proteins, IgA, lysozyme and amylase. Proteins from the parotid gland, particularly histatines, provide protection against the *Candida albicans* yeast infection for example. The submandibular gland and especially the sublingual gland make mucinous (slimy) saliva. The mucines in this saliva protect the teeth from attack by acids for example. If the function of the parotid gland is impaired, the saliva becomes thicker and more slimy, whereas impaired function of the submandibular and sublingual glands make the saliva more watery.

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Latest additions/changes

06.08.2009	full conversion to other DTP software
06.08.2009	change of spelling of Raynaud's phenomenon into Raynaud phenomenon
22.08.2009	text changes on p. 5
20.01.2010	minor text changes

Manifestations: an overview

2

Sjögren's syndrome is characterised by abnormalities and impaired functioning of the lacrimal and salivary glands. This causes symptoms of the eyes and mouth. Although in some patients with Sjögren's syndrome the abnormalities (signs) and symptomsare restricted to the lacrimal and salivary glands, other symptoms also commonly occur.[1-3] Symptoms not caused by the exocrine glands (glands that secrete fluid) are called extraglandular symptoms.

In this chapter, manifestations are described according to their frequency in Sjögren's syndrome. Some of the manifestations are also described in more detail in separate chapters, such as fatigue, fibromyalgia and neurological, gastrointestinal, hepatic, pancreatic, pulmonary and bladder disorders.

Eyes

Typical symptoms of the eyes are: burning, prickling, a gritty feeling as though there is a foreign body in the eyes and blurred vision. Itching is common but may be due to an allergy, *i.e.* for cosmetic products.

Symptoms often increase when reading and looking at a screen such as television or a computer and are the result of too little and/or abnormal tear fluid composition. Patients rarely complain of dry eyes, and if so, only after an ophthalmologist told them that their eyes were dry!

Inflammation of the salivary glands is known as *dacryoadenitis*, while the resultant inflammation of the cornea and conjunctiva is called keratoconjunctivitis sicca (KCS), see figure 2.1. Dryness of the eyes is called *xerophthalmia*.

Mouth

Typical problems of the mouth are: dry mouth (lips, tongue, throat), inability to eat dry food without drinking at the same time, difficulty in talking, damage to the teeth (dental decay around the gum line) and yeast infections. These problems are caused by too little saliva and/or abnormal saliva composition.

Inflammation of the salivary glands is called *focal lymphocytic sialoadenitis* (FLS) while the medical term for dry mouth is *xerostomia*.

In 20-50% of Sjögren's patients, one or more salivary glands are enlarged, usually unilateral and episodic.[4,5] Swelling occurring acutely or within just a few days, particularly if accompanied by redness, pain and fever, is more likely to be a (secondary) bacterial infection of the gland.[6-9]

Other features

Features other than those of the eyes and mouth are seen in differing frequency, some very commonly, others very rarely. A number of these features are discussed below, divided into categories depending on how frequently they occur.

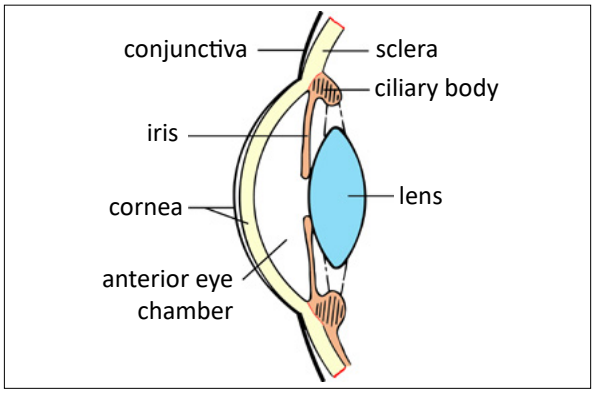

Figure 2.1 *Keratoconjunctivitis means inflammation of the cornea and conjunctiva.*

Table 2.1 Features that frequently (in more than 50%) occur

- arthralgia (painful joints)
- flu-like feeling
- myalgia (painful muscles)
- fatigue
- dry skin
- dry vagina
- *Candida albicans* infection of the mouth
- abnormal/diminished smell and taste
- functional dyspepsia
- irritable bowel syndrome

Features that frequently occur

Table 2.1 shows features that are frequently (in more than 50% of patients) seen. Fatigue, arthralgia (pain in joints) and myalgia (pain in muscles) occur in around 80-90%.[5,10-13] These symptoms may be due to an increase of interferon-activity.[81] However, it is extremely important to exclude *vitamin D deficiency* as a cause of nonspecific musculoskeletal pain. [85]

Inflammation of the joints (*arthritis*), recognisable by the swelling, heat and redness, occurs much less frequently, probably no more than 5%.[14,15]

Infection of the mouth with *Candida albicans* occurs frequently (37-75%) in Sjögren's syndrome patients.[16-20] See chapter 1 for the cause and chapter 5 for treatment.

Impaired *smell* and *taste* are common in Sjögren's syndrome patients.[87] Impaired smell occurs in 50% and is probably due to decreased mucin. Taste was significantly reduced in 70% and not affected by age. Taste threshold, unlike smell, is remarkably robust over the lifespan. Within the Sjögren's group, the finding that the threshold for sweet taste was the least reduced is almost certain because sweet taste is independent of saliva, unlike the other tastes (sour, salty and bitter).[87]

Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region, in the absence of organic, systemic, or metabolic disease that is likely to explain the symptoms.[92] The symptom complex of FD includes epigastric pain, early satiety, fullness, epigastric burning, bloating, belching, nausea, and vomiting, but there is considerable heterogeneity in the symptom pattern, both in number and type of symptoms that patients are reporting. The Rome III consensus proposed to consider only early satiation, postprandial fullness, epigastric pain and epigastric burning as typical dyspeptic symptoms.

FD has been diagnosed in 65% of patients with primary Sjögren's syndrome, as compared to in 39% of healthy controle subjects.[90]

Musculoskeletal pain

All patients with persistent, nonspecific musculoskeletal pain are at high risk for the consequences of unrecognized and untreated severe hypovitaminosis D. This risk extends to those considered at low risk for vitamin D deficiency: nonelderly, nonhousebound, or nonimmigrant persons of either sex.

Plotnikoff, Quigley (2003) [85]

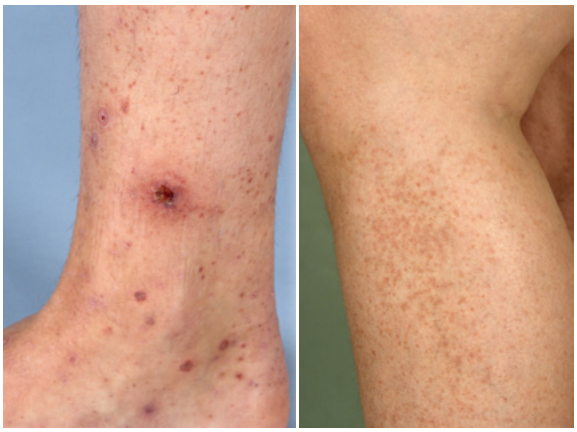

Figure 2.2 *Vasculitis in the lower legs. On the left, petechiae (bleeding into the skin) and a small wound can be seen and on the right brown flecks caused by iron residue from haemoglobin from red blood cells.*

Irritable bowel syndrome (IBS), occurring in 39-65% of patients with Sjögren's syndrome,[88,91] is a functional bowel disorder in which the key symptom of abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation. IBS was previously called *spastic bowel* or *spastic colitis* but these terms should be avoided. Functional bowel disorders are identified only by symptoms but depending on risk factors such as age, underlying diseases may have to be excluded. Subtypes of IBS are recognized by predominant stool pattern such as hard or lumpy stools, loose or watery stools, mixed and unsubtypestools. IBS is discussed in detail in chapter 9

Features that regularly occur

Table 2.2 lists features and disorders occurring in 25-50% of patients with Sjögren's syndrome.

Polyneuropathy is a condition affecting the nerve fibres, usually the sensory nerves. It causes a feeling of numbness, particularly in the feet (in the part covered

Table 2.2 Features that regularly (in 25-50%) occur

- polyneuropathy
- leukopenia
- constipation
- bronchitis sicca
- Raynaud's phenomenon
- vasculitis
- interstitial nephritis (without impaired kidney function): distal renal tubular acidosis
- deafness
- impaired gastric emptying
- gastroparesis

by socks).[21-26] See chapter on disorders of the nervous system for further details.

Leukopenia is a reduction in the number of white blood cells. This reduction is usually slight[15,27] and does not lead to infections or other consequences.

Bronchitis sicca is an inflammatory condition of the lower respiratory organs caused by dryness of the mucous membranes.[28,29]

Raynaud phenomenon causes attacks of impaired blood circulation in the hands and feet, particularly when exposed to cold temperatures. The hands and feet turn white or blue and sometimes may turn red when they warm up again.[30-33] A role of interferon in the pathogenesis of Raynaud phenomenon in Sjögren's syndrome has been suggested.[82]

Vasculitis is an inflammation of small blood vessels. In the case of Sjögren's syndrome, this mainly concerns blood vessels in the skin.[34-36] It can cause reddish blue patches (blood leakage), particularly on the lower legs, caused by blood leaking from the blood vessels (figure 2.2).

Interstitial nephritis is generally a mild (see comment below) form of inflammation around the collecting tubules in the kidneys.[37,38] This results in too little hydrogen being excreted into the urine, making the urine less acid and the body too acid (acidosis). This is known as *distal renal tubular acidosis* (DRTA) (figure 2.3). This name refers to the over-acidification of the body due to a disorder in the last section of the renal tubules. This overacidification is automatically compensated for by the lungs via (chronic) hyperventilation whereby the acid is exhaled in the form of carbon dioxide. Symptoms of hyperventilation include tingling in the hands, light-headedness, a feeling of pressure on the chest (tight chest), palpitations or involuntary yawning and sighing. Interstitial nephritis sometimes causes true kidney dysfunction.

Kidneys

The kidneys have a number of functions such as the excretion of waste substances from metabolism (*e.g.* urea and creatinine), maintaining the right volume and composition of water in the body, excretion of substances of which we have consumed more than the body needs (*e.g.* water, sodium, potassium, calcium and phosphate) and the formation of certain hormones (*e.g.* renin, angiotensin, erythropoietin and vitamin D).

In order to fulfil its functions, each kidney has about one million nephrons. A nephron consists of the glomerulus (kidney filter) and renal tubules. See figure 2.3.

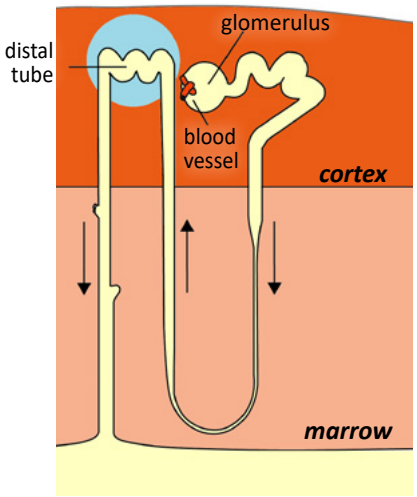

Figure 2.3 *Diagram of the nephron consisting of the kidney filter (glomerulus) and renal tubules. The area of the distal tubule is highlighted in blue.*

Deafness caused by involvement of the auditory nerve was found in a study in 14 of 30 (47%) patients with Sjögren's syndrome.[39] Nine of the 14 patients had no symptoms, the hearing loss was revealed by tests. Of the five patients with symptoms, one had severe hearing loss and four mild. There was an association between the hearing loss and antiphospholipid antibodies (see below). Other studies confirm that auditory abnormalities are frequent but clinically relevant hearing defects are not common.[40-42]

Liver diseases have been found in about a quarter of patients with Sjögren's syndrome.[75,76] These are chronic infections with HCV (hepatitis C virus) in regions with a high prevalence of HCV infection, such as the Mediterranean area (13%), and autoimmune liver diseases. Other liver diseases occur less frequently, see further and the chapter on liver and pancreatic disorders.

Impaired gastric emptying and *gastroparesis* have been diagnosed in 43% and 29% of patients with Sjögren's syndrome, respectively.[89] For further information, see chapter 9.

Features that sometimes occur

Table 2.3 shows a number of features and disorders that are sometimes seen with Sjögren's syndrome (in 5-25%).

Arthritis (inflammation of joints) occurs in 15-23% of the patients.[61] The arthritis is symmetrical and usually of the proximal interphalangeal en metacarpo-phalangeal joints of the hands and corresponding joints of the feet. Inflammation of large joints is rare. The arthritis has usually a mild course with remissions and

Table 2.3 Features that sometimes (in 5-25%) occur

- arthritis (inflammation of joints)
- non-Hodgkin's lymphoma
- interstitial lung disease
- interstitial cystitis/bladder pain syndrome
- antiphospholipid syndrome:
  thrombosis
  miscarriage
  thrombopenia
  thrombopenia
- migraine
- trigeminal neuralgial ("facial pain")
- medicine intolerance
- Hashimoto's thyroiditis
- carpal tunnel syndrome
- coeliac disease (gluten enteropathy)
- chronic atrophic gastritis

exacerbations. In contrast to the arthritis in rheumatoid arthritis, the arthritis in Sjögren's syndrome is usually non-destructive.

Non-Hodgkin's lymphoma (NHL) is a collective name for certain malignant diseases of lymphoid tissue (including lymph nodes and lymphocytes). This complication occurs in 5-8% of patients with Sjögren's syndrome, usually in salivary gland tissue and/or adjacent lymph nodes.[1,43-46,86] Baimpa *et al* conducted a retrospective study of 536 consecutive patients to assess the prevalence of hematologic abnormalities and to identify risk factors for the development of non-Hodgkin lymphoma (NHL).[86] Anemia of chronic disease and hypergammaglobulinemia were the most prevalent hematologic manifestations at diagnosis and during the course. Lymphoma was diagnosed in 7.5% of patients. Marginal zone B-cell lymphomas were the predominant histologic type (65%), while diffuse large B-cell lymphomas accounted for 17.5%. The development of NHL could be predicted by the presence of the following clinical and laboratory factors at diagnosis: neutropenia (p=0.041), cryoglobulinemia (p=0.008), splenomegaly (p = 0.006), lymphadenopathy (p=0.021), and low C4 levels (p=0.009). Patients carrying any of these factors had a more than 5-fold increased risk of NHL compared to patients with no risk factors at all.[86]

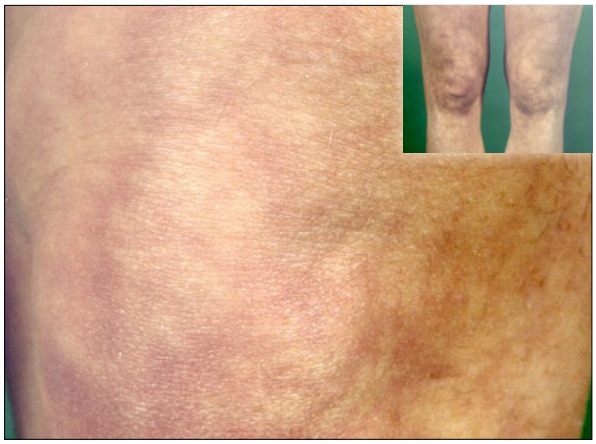

Figure 2.4 *Livedo reticularis or mottling, can often be seen above and below the knees.*

Interstitial lung diseases occur in about 25% of the patients with primary Sjögren's syndrome. Early clinical manifestations include dyspnea and dry cough. Lung diseases in Sjögren's syndrome are discussed in the chapter on pulmonary disorders.

Interstitial cystitis or bladder pain syndrome is an inflammatory bladder condition that is not caused by bacterial infection as in "normal cystitis". It may possibly be an autoimmune disease of the bladder (see chapter on urogenital disorders).[47-49]

The *antiphospholipid syndrome* has only recently been recognised as a separate entity.[50-52] It is caused by antibodies against phospholipid-associated molecules and may cause thrombosis in both veins and arteries. If this occurs in the placenta during pregnancy, it may lead to foetal death. It can also cause thrombopenia (too few blood platelets) and a skin disorder known as livedo reticularis or mottling (figure 2.4).

Thrombopenia can also occur separately from the antiphospholipid syndrome, but is likewise caused by (other) antibodies.

Thyroid disorders are more common in Sjögren's syndrome than in the general population.[5,53-55,62,84] In a recent study, 479 Hungarian patients with primary Sjögren's syndrome were investigated for the presence of thyroid disorders.[62] *Hashimoto's thyroiditis*, an inflammatory condition of the thyroid gland, was diagnosed in 30 patients (6.26%), 16 of whom had overt hypothyroidism (decreased thyroid hormone secretion) and 13 subclinical hypothyroidism (thyroid hormone secretion still normal due to increased TSH secretion). Data on Graves' disease are given in the next column.

Carpal tunnel syndrome is caused by entrapment of the nerve that regulates movement and feeling in the thumb, index finger and middle finger. This nerve (median nerve) passes through a narrow duct in the wrist which is where entrapment can occur (see chapter on disorders of the nervous system).

Chronic atrophic gastritis [56-59] is an inflammation of the gastric mucosa (stomach lining) with an increase in the number of lymphocytes and plasma cells in

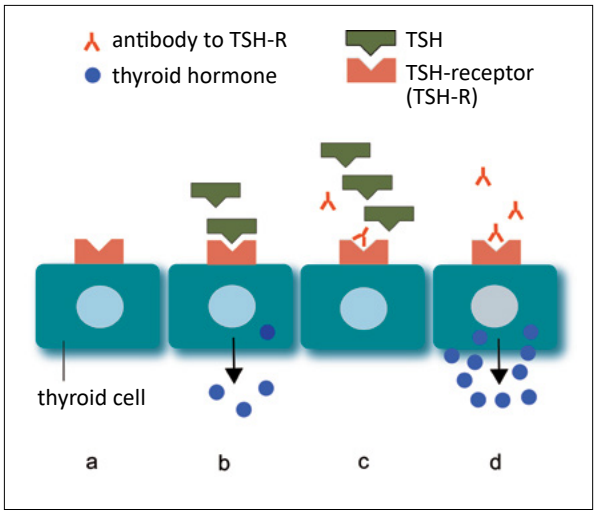

Figure 2.5 *Function of the thyroid gland.*

Normal situation. The thyroid gland cell makes thyroid hormone when TSH (thyroid stimulating hormone, an hormone synthesized and secreted by the anterior pituitary gland) binds to the TSH-receptor on the cell (b). If there is sufficient thyroid hormone in the body, less TSH is made, as a result of which the formation of thyroid hormone decreases. If there is too little thyroid hormone, more TSH is formed, leading to the formation of more thyroid hormone (thermostat principle).
Underactive thyroid gland. If there is no TSH (a) or the receptor is blocked by an antibody (c), no thyroid hormone is made; more TSH is in fact made but it cannot reach the TSH receptor: hypothyroidism.
Overactive thyroid gland (Graves' disease). If the antibody optimally slots into the TSH receptor (d), the thyroid gland cell is stimulated into making thyroid hormone (hyperthyroidism) independently of the (low) TSH level.

the tissue. As a result, the glands in the stomach lining are damaged and reduced in number (atrophy). The involvement of parietal cells (figure 2.6) leads to a reduction in the formation of hydrochloric acid (*achlorhydria*) and intrinsic factor (IF). Since IF is necessary for absorption of vitamin B12 further along in the small intestine, this leads to pernicious anaemia. *Pernicious anaemia* can also be caused by antibodies against IF, likewise preventing absorption of vitamin B12. However, pernicious anaemia occurs in fewer than 5% of patients with Sjögren's syndrome.

Coeliac disease (gluten sensitive enteropathy) is characterized by small-intestinal mucosal injury and nutrient malabsorption in genetically susceptible individuals in response to the dietary ingestion of wheat gluten and similar proteins in barley and rye. Coeliac

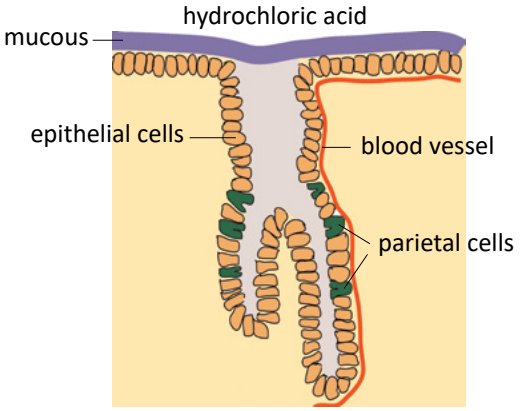

Figure 2.6 *Gland of the gastric mucosa with parietal cells. Parietal cells produce hydrochloric acid and intrinsic factor.*

disease affects about 1% of the population but only 10-15% of these individuals have been diagnosed and treated.[77] See chapter on gastrointestinal disorders.

Features that rarely occur

Table 2.4 shows features and disorders that rarely (in fewer than 5%) occur in Sjögren's patients.

Graves' disease, a thyroid disease caused by autoantibodies to the TSH-receptor (figure 2.5) with hyperthyroidism or subclincal hyperthyroidism was diagnosed in 3.76% of the Sjögren patients, a prevalence not different from that in the general

Table 2.4 Features that rarely (in fewer than 5%) occur

- autoimmune hepatitis (2%)
- glomerulonephritis
- Graves' disease (4%)*
- interstitial nephritis with impaired kidney function
- lymphocytic interstitial pneumonia
- myasthenia gravis
- osteomalacia
- pancreatitis (inflammation of the pancreas)
- pernicious anaemia
- primary biliary cirrhosis (4%)
- prostatitis
- pulmonary arterial hypertension
- sclerosing cholangitis
- small fibre neuropathy (3%)
- uveitis

**not statistically different from the prevalence in the general population.*

How to deal with features that may possibly form part of Sjögren's syndrome

Sjögren's syndrome does not offer protection against other diseases and disorders. A Sjögren's patient consequently has the same risk of developing other diseases and disorders as anyone else. Do not therefore be tempted to attribute everything to Sjögren's syndrome.

The disadvantage of doing this is that the true cause may never be found and usually no solution either. When faced with features that cannot automatically be attributed to Sjögren's syndrome, the best approach is first to have it investigated.

Only when a diagnosis has been made should you examine the possibility of a relationship with Sjögren's syndrome. This can best be explained on the basis of an example.
Imagine that someone with Sjögren's syndrome has had stomach pain for 6 weeks and is anaemic. A few possible causes could be a gastric or duodenal ulcer, stomach cancer, inflammation of the gastric mucosa (lining of the stomach) due to the use of certain anti-inflammatory drugs, or chronic atrophic gastritis. The correct diagnosis can only be reached after inspection of the stomach using a flexible camera (gastroscopy). This investigation has to be carried out by an experienced doctor who can interpret the results.

A gastroscopy allows the oesophagus, stomach and duodenum to be inspected while small pieces of tissue can be removed (biopsy) for microscopic examination from areas here abnormalities are seen.
Once a diagnosis has been made, it can then be interpreted in relation to the Sjögren's syndrome. Generally speaking, this can only be done properly by a doctor with experience of Sjögren's syndrome. In the case of stomach cancer, there is no direct relationship with Sjögren's syndrome. Erosion (superficial damage to the gastric mucosa) or gastric ulcers may be the result of certain anti-inflammatory drugs (see also chapter 5). Where chronic atrophic gastritis is concerned, a relationship with Sjögren's syndrome can be considered likely.

In other words, correct interpretation can only take place if a diagnosis has first been made without the features immediately being associated with Sjögren's syndrome.

Don't let Sjögren's syndrome be blamed for everything! Be on your guard when someone without real knowledge of Sjögren's syndrome blames an unidentified complaint on Sjögren's syndrome.

population.

Primary biliary cirrhosis is the most frequent (4%) autoimmune liver disease in Sjögren's patients. Less frequent is autoimmune hepatitis (2%).[75,76] The clinical picture of autoimmune hepatitis may vary from asymptomatic to fulminant liver failure. See chapter on liver and pancreatic disorders).

Lymphocytic interstitial pneumonia (LIP)[60] is an

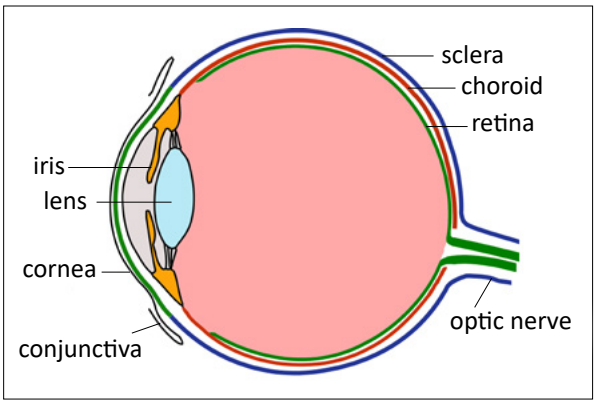

Figure 2.7 *Structure of the eye (see text).*

inflammation around the small bronchial tubes in the lungs that resembles the inflammation found in the lacrimal and salivary glands. It is a serious complication that is treated with prednisolone and/or other drugs that suppress the immune system (see chapter on pulmonary disorders).

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries with vascular proliferation and remodeling, resulting in a progressive increase in pulmonary vascular resistance and right ventricular failure. Right-heart catheterization is the gold standard for the diagnosis. PAH has a poor prognosis but treatment options have progressed strikingly recently [78] (see chapter on pulmonary disorders).

The tissue of the pancreas and prostate gland shows some similarity with that of the salivary glands. In rare cases, these organs may be enlarged and/or inflamed in Sjögren's syndrome (*autoimmune pancreatitis*; [63,64] *nonbacterial prostatitis* [82]).

Myasthenia gravis is an autoimmune disease in which the control of the muscles by the nerves is affected.[65,66] This disease is generally caused by antibodies against the acetylcholine receptor. The

Table 2.5 Features of which the relationship with Sjögren's syndrome has not been proven

- depression
- sarcoidosis (Besnier-Boeck disease)
- organizing pneumonia (old name: bronchiolitis obliterans organizing pneumonia, BOOP)
- dizziness
- impaired concentration

symptoms are mainly muscle weakness and fatigue (see chapter 7).

Interstitial nephritis is usually a mild disorder of the renal (kidney) tubules. In rare instances, the kidney function may be decreased.[67-69]

Glomerulonephritis (inflammation of the kidney filter) can decrease the kidney function, but is rare in patients with Sjögren's syndrome. In these cases, the question to be considered is whether the patient might not in fact (also) have systemic lupus erythematosus.

Uveitis is inflammation of the uvea of the eye. The uvea consists of the iris, ciliary body and choroid, see figure 2.7. The different parts of the uvea may be inflamed separately or together. Anterior uveitis (iridocyclitis) is inflammation of the front parts of the uvea, iris and ciliary body. Posterior uveitis (choroiditis) is inflammation of the back part of the uvea: the choroid. *Panuveitis* is inflammation of both the front and back parts of the uvea. The symptoms of uveitis may consist of light intolerance, blurred vision, pain and redness of the eye. Uveitis may present itself suddenly with redness and pain in the eye, but can also occur slowly with increasingly blurred vision but only a little pain or redness.[70,71]

Osteomalacia (softening of the bones) is a bone disorder, comparable with rickets in children. Symptoms are pain in the bones and fractures. There are various possible causes such as calcium, phosphate or vitamin D deficiency, acidosis and certain drugs. It is a rare disorder in Sjögren's syndrome, but is associated with distal renal tubular acidosis (see above).[72-74]

Small fibre neuropathy occurs in about 3% of patients with Sjögren's syndrome.[79] It is a peripheral neuropathy characterized by the impairment of thinly myelinated A and unmyelinated C-fibres. Both somatic and autonomic fibres may be involved, thus leading to sensory and autonomic neuropathies. Isolated autonomic neuropathies are rare. Symptoms of somatic nerve fibre dysfunction, such as burning, pain, and hyperaesthesia, frequently prevail over those related to autonomic nerve fibre impairment. This may explain why the term "painful neuropathy" is often used as a synonym (this is not correct as painful symptoms can also be a feature of large fibre neuro pathies).[80]

Features of which the relationship with Sjögren's syndrome is uncertain

Table 2.5 shows common disorders where the relationship with Sjögren's syndrome is uncertain.

Depression is by no means rare but the relationship with Sjögren's syndrome is not certain.

Sarcoidosis (Besnier-Boeck disease) is discussed in chapter 20, questions 37 and 43, and organizing pneumonia in the chapter on pulmonary disorders.

Dizziness can have many causes, such as hyperventilation, that may be indirectly related to Sjögren's syndrome.

Impaired concentration commonly occurs but it is uncertain whether this is due to Sjögren's syndrome. It may be caused by fatigue. Since acetylcholine and muscarinic receptors (see chapter 3) play a role in storing information in the memory, this could be a possible explanation.

The relationship between Sjögren's syndrome and other generalized autoimmune diseases.

Sjögren's syndrome sometimes occurs in combination with other generalized autoimmune disease (see table 2.6). It is then often referred to as secondary Sjögren's syndrome. This only means that there are two diseases present and not that the Sjögren's syndrome is the consequence of the other disease.

The generalized autoimmune diseases mentioned

Table 2.6 Generalized autoimmune diseases that may occur in combination with Sjögren's syndrome

disease	*characteristic feature*
- rheumatoid arthritis	way it affects the joints
- systemic lupus erythematosus (SLE)	way it affects the skin
- subacute cutaneous lupus erythematosus (SCLE)	way it affects the skin
- mixed connective tissue disease (MCTD)	specific combination of features and antibodies to RNP
- systemic sclerosis (scleroderma)	way it affects the skin
- CREST syndrome (limited systemic sclerosis)	specific combination of features

have many features in common. Features that may occur in both Sjögren's syndrome and the diseases listed in table 2.6 include inflammation of the joints (arthritis), Raynaud phenomenon, vasculitis and lowered white blood cell count (leukopenia). Just as Sjögren's syndrome is characterised by the effect on the (function of the) lacrimal and salivary glands, each of the other generalized autoimmune diseases is characterised by its own specific features.

Patients with a specific generalized autoimmune disease may greatly differ in the non-specific features they may have. There are good arguments for the current system of classifying generalized autoimmune diseases, for example in connection with expected damage and the best treatment. However, the diseases mentioned occur so frequently either in combination or in intermediate forms that the question arises as to whether we are really dealing with two separate diseases here. It is possible that there may be one disease with features that fall within the definition of two diagnoses.

The way in which generalized autoimmune diseases are classified is principally a question of mutual agreement and consensus. The current classification and definitions will undoubtedly change in the future on the basis of results of scientific research.

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Latest additions or modifications (date: dd.mm.yyyy)

date	***addition/modification***
09.01.2009	prevalence of Hashimoto's thyroiditis and Graves' disease in Sjögren's syndrome
24.08.2009	added musculoskeletal pain as a result of severe vitamin D deficieny; ref 85
14.09.2009	non-Hodgkin lymphoma predictors; ref 86
30.09.2009	data on abnormal/diminished smell and taste perceptions; ref 87
21.09.2010	prevalence of irritable bowel syndrome in Sjögren's syndrome added; ref 88
21.09.2010	prevalence of impaired gastric emptying and gastroparesis in Sjögren's syndrome added; ref 89
03.10.2010	prevalence of irritable bowel syndrome and tables updated; ref 91 information added on functional dyspepsia; ref 90,92

Cause

3

The eye and mouth symptoms in Sjögren's syndrome are caused by abnormalities in tear fluid and saliva. A criterion for diagnosis is usually inflammation found in the lip biopsy. So it goes without saying that this inflammation is found in virtually everyone with Sjögren's syndrome. It therefore seems logical for the inflammation in the glands to be the cause of the symptoms. Later in this chapter another possible cause of the abnormalities in the tear fluid and saliva will be discussed.

Despite questions that have arisen concerning the role of inflammation in the glands, in many patients inflammation is present. The cause of this is unknown. Obvious causes such as bacterial or viral infection have not as yet been proven.

When discussing the cause of a disease, it is useful to draw a distinction between what causes someone to get the disease (*aetiology*) and how the symptoms of the disease come about (*pathogenesis*).

Nothing is known about the aetiology. We know that several hereditary characteristics, including gender and certain genes, have an influence on the risk of developing the disease.

More is known about the pathogenesis, but the first stages are unclear.

Sjögren's syndrome is considered to be an autoimmune disease. The term *autoimmune disease* is explained in the box on the next page.

Genetic factors

The development of a genetic disease is entirely determined by genetic factors. Inheritance usually follows clear patterns and in the case of *identical* twins either both or neither has the disease. None of this applies to Sjögren's syndrome. Sjögren's syndrome is therefore not a genetic disease. However, the chance of developing the disease is nevertheless partially determined by genetic factors, while environmental factors probably also play a role. Although a few genetic factors are known, the environmental triggers are not.

Female sex

The largest genetic risk for Sjögren's syndrome is the female sex as 90% of patients with Sjögren's syndrome is female. This female preponderance is likely based on genes located in sex chromosome 23: having two X chromosomes and/or missing the Y chromosome.

A parent has Sjögren's syndrome

The risk for autoimmune diseases is higher than normal for children of patients with Sjögren's syndrome. The risk is higher if the parent is the mother who has the disease.

Table 3.1 Genes that increase the risk of developing Sjögren's syndrome

gene	*prevalence (%)*		
	healthy subjects	*Sjögren patients*	*relative risk*
HLA A24 [46]	12	33	2.5
HLA B8	19	59	3
HLA DR3	23	66	2.4
HLA DR52	53	81	1.6
STAT4 SNP [a] rs7574865 [44,48]	20.8-23.7	29.6 [c]	1.3
HLA DR3-RCAa block epistatic interaction [45]	8	48 [b]	6
immunoglobulin-like transcript 6 [51]	3	8	2.7

[a] SNP: single nucleotide polymorphism
[b] patients with antibodies to SSA/Ro and SSB/La
[c] the same haplotype has been found in chromosomes of patients with rheumatoid arthritis (24.7-28.9%) and systemic lupus erythematosus (31%) [47,48]

Autoimmune diseases

The immune system normally only attacks foreign substances from outside the body. However, small changes on the outside of our own cells can be recognised as foreign by our immune system and subsequently killed. This is usually a good thing since abnormal cells can form a danger, *e.g*. malignant cells or cells containing a virus.

The immune response is sometimes directed against a microorganism and the antibodies and/or T lymphocytes may crossreact with the body's own components. The background to this is a similarity between proteins or sugar compounds of micro-organisms and components of our own body.

The question as to whether a specific disease is an autoimmune disease or not can only be answered after first establishing what we mean exactly by the term autoimmune disease. In the case of many so-called autoimmune diseases, there is no indication that the immune system is not in order. All that can be shown or assumed is that the immune system is involved in damage to cells and tissue.

In many infectious diseases, the immune system is responsible for the disease symptoms and not the microorganism itself. An example of this is *hepatitis B* in which the inflammation of the liver is mainly the result of the immune system's response to the presence of the virus. *Tuberculosis* is an example of the same process in the case of diseases caused by bacteria. If, however, the pathogenic organism (bacterium or virus) causing the disease is known, the disease is no longer considered to be an auto-immune disease. Infectious diseases in which the damage is mainly caused by the response of the immune system (that can greatly vary from person to person) are particularly striking for the greatly varying, often relatively late consequences of the infection. Usually only a small percentage of the infected people develop the disease and with varying severity. People who are unlucky in this respect where certain micro-organisms are concerned may suffer no ill-effects from others. This is important for the survival of the species because when an epidemic occurs there are always some people who survive the disease or never catch it at all.

There are only a small number of diseases without a known pathogenic organism, where it has been proven that the symptoms are caused by the immune system. These are mainly diseases caused by antibodies. There are diseases that pregnant women with antibodies can transmit to the child in the womb via the placenta. Children retain antibodies from their mother for about 6 months after their birth. These antibodies protect them from infection for as long as they are unable to make the antibodies themselves.

However, if the mother has antibodies that could cause symptoms of disease, the children may also manifest these symptoms. Examples of these are certain thyroid disorders, myasthenia gravis and neonatal lupus that are caused by antibodies against the TSH-receptor on thyroid cells, antibodies against the acetylcholinereceptor on muscle cells and antibodies against SSA/Ro and/or SSB/La. When the mother's antibodies disappear in the child, the disease symptoms in the child also disappear.

The fact that antibodies against the body's own components are found in a specific disease does not mean that it is an autoimmune disease, not even if they precede the disease. For example: antibodies against the islets of Langerhans in the pancreas are the result of damage to these islets, usually many years before the number of islets has decreased to such an extent that *diabetes mellitus* manifests itself. Diabetes mellitus is in fact probably an autoimmune disease but caused by a different mechanism. A disease is usually considered to be an autoimmune disease if it complies with a number of criteria (see below).

Characteristic features considered to be an indication of the autoimmune nature of a specific disease (examples)

- no micro-organism or other cause has been found for the disease
- the disease occurs more often in certain families
- the disease occurs more often in people with certain genes of the HLA system
- the disease occurs more often in women than in men
- antibodies against the body's own components occur in many or all of the patients with the disease
- the disease can sometimes be transmitted from mother to child in the womb
- the patient / relatives of the patient often also has / have another disease that is considered to be an autoimmune disease
- in the case of experimental animals, it is sometimes possible to stimulate the disease in other identical experimental animals by transferring antibodies or lymphocytes
- the disease can be "treated" with drugs that have an effect on the immune system or inflammatory response

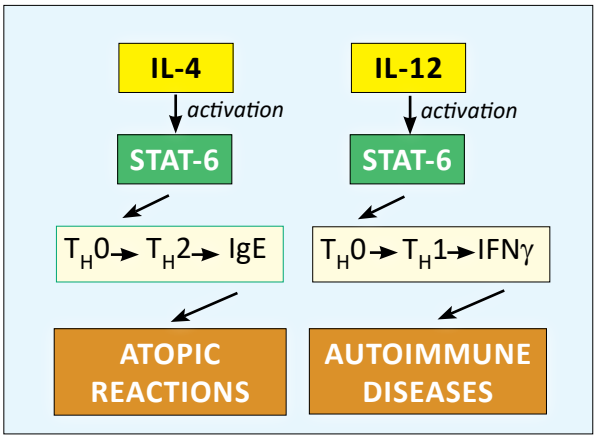

Figure 3.1 *Simplified scheme of differentiation of naive T lymphocytes (T_H0) into T_H1 or T_H2 lymphocytes.*

HLA genes

Certain genes from the HLA or other systems increase the risk of developing the disease. Table 3.1 shows how often some of these occur in normal healthy people and how often in Sjögren's syndrome patients. However, their influence on the chance of developing Sjögren's syndrome is slight.

STAT 4 genes

Recent findings on STAT4 are interesting. An increased incidence of the haplotype rs7574865 has been found in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome.[44,47,48] Homozygosity is associated with a more than doubled risk of SLE and a 60 percent increased risk of RA.[47]

The JAK/STAT pathway is the signaling target of a multitude of cytokines that are thought to play biologically significant roles in inflammation. STAT4 transmits signals induced by IL-12, IL-23, and type I interferons (IFNs). A major action of IL-12 through STAT4 signaling is to promote the differentiation of naive $CD4^+$ T lymphocytes into T_H1 cells, which produce IFN. These T_H1 cells are thought to drive the chronic autoimmune response (figure 3.1).

STAT4 is also important for the development of the recently identified IL-17 secreting T helper cells, which are stimulated by IL-23. These T_H17 cells play critical roles in autoimmune diseases through the production of IL-17. T_H17 cells have been found to be the predominant infiltrating T cell in the salivary glands of patients with Sjögren's syndrome.[49]

Immunoglobulin-like transcript family

Immunoglobulin-like transcript (ILT) genes are located in the leukocyte receptor complex on chromosome 19 and consist of 13 homologous receptors with activating and inhibiting capacity. ILTs are mainly expressed on antigen-presenting cells (macrophages, dendritic cells and B lymphocytes. ILT2 is also expressed on NK cells and T-lymphocytes.

ILT6 is expressed only as a soluble molecule, but its presence is variable. *Homozygous deficiency of ILT6* has been shown to be absent in 7.3% of multiple sclerosis patients but in only 3% of normal blood donors.

Kabalak *et al* [51] investigated 149 patients with Sjögren's syndrome and 749 healthy blood donors for homozygous presence, homozygous deletion and heterozygous deletion of ILT6. Homozygous ILT6 deletion was found to be associated with Sjögren's syndrome (8% in patients versus 3% in controls, $p<0.01$). The authors speculate on possible mechanisms. They suggest that absence of ILT6 may cause enhanced destruction of gland cells by $CD8^+$ T cells. The authors realize, however, that the majority of infiltrating lymphocytes are $CD4^+$ T cells and B cells. Exocrine glands, however, are not usually destroyed in Sjögren's syndrome but mainly functionally defect. Gland destruction may occur in some patients but this is usually due to recurring secondary bacterial infection of the glands due to duct obstruction by viscous secretions (see further). A second explanation suggests that antiviral defense is impaired due to ILT6 deficiency. The authors cite data on the possible role of Epstein-Barr virus and coxsackievirus in triggering Sjögren's syndrome.[51] The possible role of these viruses, however, is not supported by clinical evidence.

Drugs

Many cases have been described on various drugs that can induce SLE, but reports on drug-induced Sjögren's syndrome are very rare.

Darwaza *et al* [52] described a 60-year-old male patient who developed clinical features of Sjögren's syndrome, with immunological features of drug-induced SLE, 4 years after initiation of therapy with hydralazine hydrochloride (for treatment of hypertension). The patient had reduced lacrimal and parotid salivary flow, but lacked the typical features of Sjögren's syndrome on labial gland biopsy. One year after discontinuation of hydralazine therapy, the clinical parameters returned to normal.

Onishi *et al* [53] described a 57-year-old Japanese woman who developed skin eruption, pleuritis, pancytopenia, parotid gland swelling and glomerulonephritis after 7-month treatment with pegylated interferon-α and ribavirin for chronic hepatitis C. Disease-specific autoantibodies such as

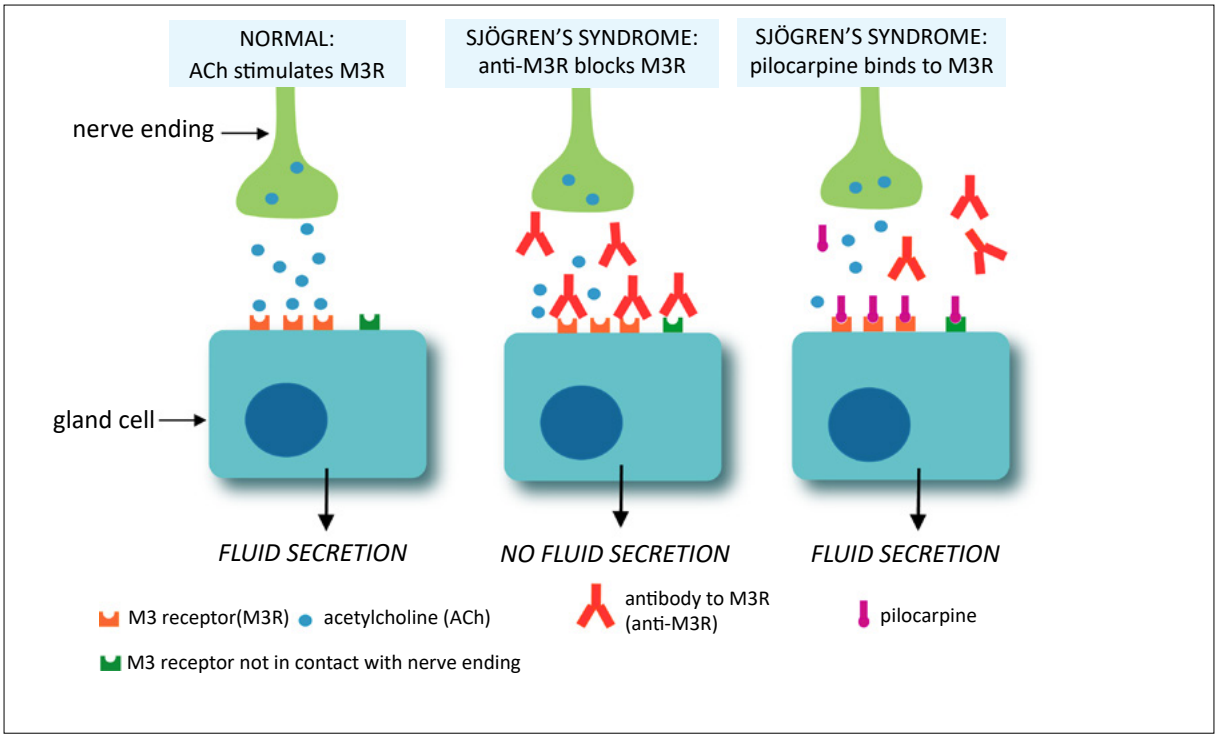

Figure 3.2 *Diagram of the hypothetical cause of dryness symptoms in patients with Sjögren's syndrome. Autoantibodies against the M3 receptor (M3R) block the binding of acetylcholine to the M3R. Pilocarpine binds to the M3R despite the antibodies. Note that pilocarpine also binds to M3 receptors that do not normally bind to acetylcholine. This may explain the effect of pilocarpine regardless of any role by antibodies.*

anti-SSA, anti-SSB, anti-Sm and anti-dsDNA antibodies became positive. The diagnosis of SLE and Sjögren's syndrome was made and treatment with glucocorticoid pulse followed by oral glucocorticoid was started. The authors conclude that it is highly probable that interferon-α induced SLE and Sjögren's syndrome in this case.

In both cases, Sjögren's syndrome was diagnosed in addition to SLE, suggesting that the mechanisms of these drug-induced diseases are similar.

Table 3.2 Causes of disease symptoms in Sjögren's syndrome

- autoantibodies
- immune complexes
- focal lymphocyte infiltration
- malignant proliferation of lymphocytes (non-Hodgkin lymphoma)
- consequences of dry mucous membranes
- electrolyte imbalance (hypokalemia, acidosis)

Pathogenesis

Table 3.2 shows a number of ways in which the disease symptoms may be caused.

Regulatory T lymphocytes

Regulatory T lymphocytes (T_{reg} cells) represent about 5% of $CD4^+CD25^+$ T cells. Treg cells play a critical role in the mediation of a suppressive function and in maintaining a broad range of T-cell antigen receptor specificities that prevent the development of autoimmune responses. T_{reg} cells thus are the main cells that maintain the immune homeostasis in the periphery and regulate autoimmunity. The percentage of T_{reg} cells has been found to be about three times lower in patients with SLE, systemic sclerosis, Sjögren's syndrome and poly myositis/ dermatomyositis than in healthy controls.[50] The percentage of particular subsets ($GITR^+$ T_{reg} cells) was higher in Sjögren's patients with antibodies to SSA/Ro than in those without. Treatment was correlated with lower percentages of particular subsets of T_{reg} cells.

Future studies are needed to understand the relevance of these findings and to find out whether they play a

Table 3.3 Classification of immunological responses according to the recognised antigen and significance

antigen	*significance*
bacterium, virus	resistance
harmless external substances	allergy
body's own components	autoimmune disease

Table 3.4 Possible autoantibodies in Sjögren's syndrome and disease features

autoantibodies to	*disease feature*
SSA/Ro and/or SSB/La	sensitive to sunlight neonatal lupus in children
granulocytes	too few granulocytes
blood platelets	too few blood platelets
red blood cells	breakdown of red blood cells
"phospholipids"	antiphospholipid syndrome
thyroid TSH-receptor	hyper- or hypothyroidism

primary role or merely result from the disease, disease activity or treatment.

Autoantibodies

Autoantibodies recognise the body's own components. The function of antibodies is recognition and provoking a response from proteins or cells. Antibodies can be formed against virtually every substance and this substance is known as an antigen. If antibodies later encounter the antigen again (recognition), the consequences depend on the nature of the antigen (table 3.3). If the antibodies recognise components of a virus or bacterium, this creates resistance to the infectious disease concerned. If the antibodies are directed at harmless external substances (*e.g.* pollen), the response is called an allergy. If the antibodies damage the body's own cells, we call this an autoimmune disease (T lymphocytes may also give similar responses).

Autoantibodies to SSA/Ro and SSB/La

The best known autoantibodies in Sjögren's syndrome are those against SSA/Ro and SSB/La.[1-4] These are proteins that occur in every cell of our body and play a role in the division of cells. Although it is not certain whether these antibodies can cause disease symptoms in Sjögren's patients, they may possibly increase the skin's sensitivity to sunlight.[5] When women with these antibodies are pregnant, the antibodies also reach the foetus. There is then an approximately 10% risk of the baby developing neonatal lupus.[6,7] The most common symptoms are skin disorders (that subside of their own accord) while the most serious complication that can occur is congenital heart block.[8,9] Neonatal lupus is discussed in more detail in chapter 11.

Table 3.4 shows a number of consequences of the occurrence of specific autoantibodies in Sjögren's syndrome. Granulocytes are certain types of white blood cells (see chapter 15, Clinical investigations). Antiphospholipid antibodies are discussed in the chapter 13 on pregnancy and lactation.

Autoantibodies against muscarinic M3 receptors

Based on a specific strain of mice (NOD mice) that develops diseases such as Sjögren's syndrome, American scientists have developed a mouse without B-lymphocytes.[29] B-lymphocytes are the white blood cells that make antibodies after maturing into plasma cells. In other words, these mutated mice make no antibodies. Like the normal NOD mice, they developed typical lymphocyte infiltrates in the salivary and lacrimal glands but made normal saliva and tears. This was striking since it was believed to be the infiltrates that caused the dryness. It was then seen that if antibodies from normal NOD mice or patients with Sjögren's syndrome were injected into the mice without B-lymphocytes, they then developed symptoms of dryness. This therefore means that it was the antibodies that caused the reduction in fluid secretion and not the inflammation in the glands. It was shown to concern antibodies against muscarinic M3 receptors that are present in cells in the lacrimal and salivary glands. The glands normally secrete fluid when acetylcholine (ACh) is released from nerve ends and binds to the M3 receptor (see figures 3.2 and figure 7.2).[30,31]

Autoantibodies to the M3 receptor in the sera of patients with Sjögren's syndrome recognise and bind to the M3 receptors of salivary glands in normal human people and patients with Sjögren's syndrome *in vivo*.[42] In recent years, various different researchers have attempted to demonstrate the presence of antibodies against M3 receptors in the blood of patients with Sjögren's syndrome. This has only been successful for research purposes. No test is available that can be used in clinical practice to date.

Pilocarpine

Pilocarpine is a drug that binds to M3 receptors, causing the glands to be stimulated into producing fluid. This

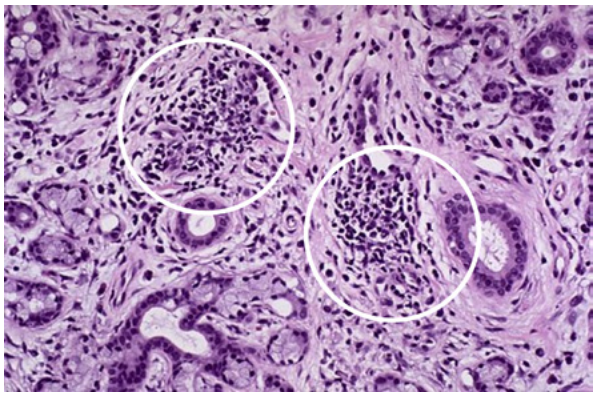

Figure 3.3 *Salivary gland tissue specimen with two focal infiltrates, indicated by white circles.*

probably also concerns M3 receptors that are not normally reached by acetylcholine from the nerves (see figure 3.3).[12,32] Pilocarpine has been known for several hundred years and was discovered by South American Indians who chewed on the leaves of the *Pilocarpus jaborandi* shrub if they had a dry mouth. In 50-60% of Sjögren's patients, use of pilocarpine leads to a decrease in dryness. Cevimeline is another new substance with the same effect, but is not available in Europe. Pilocarpine not only increases fluid production in lacrimal and salivary glands. Other exocrine glands and smooth muscle tissue may also respond to the drug. This is why some patients experience side effects such as sweating and a need to urinate more frequently (there are also M3 receptors in the bladder muscle). In some patients, pilocarpine helps the eyes but not the mouth, or vice versa. There are also people whose only response is to sweat.[33-39]

It is possible that the different effects of pilocarpine may be connected with small differences in the M3 receptors of organs and between individual people. If this hypothesis is correct, it could also explain the different forms of Sjögren's syndrome occurring in different people.

Autoantibodies to 120 kD α-fodrin

Japanese scientists have discovered that a certain strain of mice in which the thymus is removed 3 days after birth develops Sjögren's syndrome.[40] They also found that these mice have antibodies and T-lymphocytes that react with 120 kD α-fodrin, a fragment of 240 kD α-fodrin. 240 kD α-fodrin is a protein that particularly plays a role in fluid secretion by cells, but also occurs in the membrane of most cells in the body. The scientists then injected 120 kD α-fodrin into the mice without a thymus. The result was that these mice did not develop Sjögren's syndrome.

120 kD α-fodrin is also found in the salivary glands of Sjögren's patients, but not in healthy people. The anti bodies and T-lymphocytes in the patients recognise the 120 kD α-fodrin, but not the 240 kD α-fodrin.

α--Fodrin also plays a role in *apoptosis*. Apoptosis is a process whereby a cell "switches itself off" in order to die. If a cell goes into apoptosis too soon, this is harmful because the cell is still young, not yet mature and not yet fully functional. Nor it is good if apoptosis takes place when the cell is too old, since damage can be caused by disruption to or loss of function. In other words, apoptosis needs to take place at exactly the right moment. In the case of apoptosis in patients with Sjögren's syndrome, scientists suspect that too

Muscarine and the Death of the Roman Emperor Claudius

The Roman emperor Claudius (figure 3.4) died unexpectedly on 13 October AD 54. He had just eaten a meal, drunk a considerable amount of wine and rounded off the repast with a favourite Roman dish of mushrooms. As an extra delicacy, he was given an additional large mush room, probably through the intervention of his wife Agrippina.

After eating, Claudius developed severe abdominal pain with vomiting, diarrhoea, extreme salivation, respiratory problems and incontinence. He died 12 hours later.

In view of what happened, his extra delicacy must have been *Amanita muscaria* or Fly Agaric (figure 3.5).[a]

Figure 3.4 *Claudius and Agrippina*

This mushroom contains the poison muscarine.

Muscarine can strongly bind to certain acetylcholine receptors AChR). These receptors are therefore known as muscarinic receptors (the other AChR bind to nicotine and are called nicotinic receptors). When taking pilocarpine, however, there is no need to be afraid of suffering the same fate as Claudius. Pilocarpine binds much shorter and weaker to the muscarinic receptors than muscarine and is most definitely not a dangerous substance.

[a] Matt Pueschel. Claudius Likely Victim Of Poisonous Mushroom. US Medicine, March 2001 http://www.usmedicine.com(accessed 2001)

Figure 3.5 *The mushroom Amanita muscaria (Fly Agaric) that contains the poison muscarine (front cover of the book: Dr Jac. P. Thijsse. Paddenstoelen (Mushrooms). Published by Verkade's Fabrieken N.V., Zaandam 1929).*

much 120 kD α-fodrin is being formed. Many Sjögren's patients appear to have antibodies against 120 kD α-fodrin. More research is necessary to discover the exact significance of this.

Immune complexes

Immune complexes are complexes of antibodies, complement proteins and antigens. The formation of immune complexes is normal and is a way in which the body disposes of superfluous substances, *e.g.* bacterial residue. Depending on the composition of the immune complexes (type of antibody and antigen, size) they can be formed in the wall of blood vessels, resulting in inflammation of the blood capillaries (vasculitis). This is usually visible in the form of large or small haemorrhages in the skin (petechiae or purpura, respectively) on the lower legs.

Focal lymphocytic infiltration

Focal lymphocytic infiltration (localised clusters of lymphocytes) not only occurs in the lacrimal and salivary glands (figure 3.3), but may also occur in other organs such as the stomach, pancreas and kidneys. In the lip biopsy this is expressed as the focus score. A focus is a cluster of 50 or more lymphocytes and the focus score is the number of these foci in a 4 mm^2 section of tissue.[10,11]

The contribution of the infiltrates to the functional impairment and damage to the glands is uncertain. It probably is far less the case than people think. Whereas 53% of the surface of a lip tissue specimen normally consists of gland cells, in the case of Sjögren's patients this is 34%.[12] Figure 3.2 shows the lip tissue specimen (with a focus score of 4) of a Sjögren's patient with a very dry mouth. These data indicate that the infiltrates cannot be the only cause of the decrease in saliva formation. Experience with pilocarpine (see further) reinforces the idea that it may well be more complex than hitherto thought. On the other hand, focal lymphocytic infiltration may also be found in healthy people without complaints of dryness of the mouth. The frequency of focal lymphocytic infiltration in healthy volunteers has been found to be 15%. The positive focus score ranged from 2 to 6 and did not correlate with age, smoking, serologic findings or salivary flow in these persons.[41]

In a recent examination of inter-rater reliability for a group of 5 board-certified pathologists interpreting the same series of labial salivary gland biopsies, the agreement was found to be uniformly poor for judgments of diagnostic status, focus scores, and histological characteristics of biopsy specimens. This lack of reliability is troubling.[43]

Lymphomas

5-8% of Sjögren's patients develop a malignant non-Hodgkin's lymphoma in places where focal lymphocytic infiltrates are present.[13-17] This is about 44x higher than the normal risk. The lymphoma usually is a MALT lymphoma caused by lymphocytes in the mucous membranes.[18] Treatment of lymphomas depends on the type of lymphoma. The prognosis for MALT lymphomas is relatively favourable in comparison with other forms of lymphoma.[18]

Consequences of dry mucous membranes

Dry mucous membranes can themselves be the cause of disorders. The lack of adequate saliva can lead to cervical caries (gum line tooth decay) [19-21] and oral infections with Candida albicans (a yeast or single-cell fungus).[22,23]

The bacterium *Streptococcus mutans*, that plays a role in tooth decay, is found in greater numbers in the mouth of a Sjögren's patient.[24]

Electrolyte imbalance

The presence of lymphocyte infiltrates around the renal tubules (interstitial nephritis) may be accompanied by inadequate excretion of hydrogen. The urine

consequently becomes less acid than normal, while too much acid remains behind in the body (acidosis). As a result of the acidosis, the lungs automatically begin to hyperventilate and this in turn can cause symptoms such as tingling in the hands and feet, a tight feeling in the chest, palpitations, headache, light-headedness and frequent yawning and sighing. Instead of hydrogen, the kidneys excrete more potassium. This can lead to potassium depletion with temporary symptoms of paralysis.[25-28]

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Latest additions or modifications (date: dd.mm.yyyy)

date	***addition/modification***
11.08.2009	conversion for another DTP program
01.10.2009	ref 51 Ig-like transcript 6 deficiency
15.01.2010	ref 52-53 drug-induced Sjögren

Scand J Rheumatology 1986; Suppl. 61: 19–21

The Copenhagen Criteria for Sjögren's Syndrome

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Scand J Rheumatology 1986; Suppl. 61: 28–30

First International Symposium on Sjögren's Suggested Criteria for Classification*

Annals of the Rheumatic Diseases 1996; 55: 116–121

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Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study

Claudio Vitali, Stefano Bombardieri, Haralampos M Moutsopoulos, Joaquin Coll, Roberto Gerli, Pierre Y Hatron, Louis Kater, Yrjö T Konttinen, Rolf Manthorpe, Olivier Meyer, Marta Mosca, Pierantonio Ostuni, Raffaele A Pellerito, Yvon Pennec, Stephen R Porter, Andrea Richards, Bernard Sauvezie, Morten Schiødt, Maria Sciuto, Yehuda Shoenfeld, Fotini N Skopouli, Josef S Smolen, Francisco Soromenho, Moshe Tishler, Matija Tomsic, Joop P van de Merwe, Christine M Yeoman, Marie J Wattiaux (The European Study Group on Diagnostic Criteria for Sjögren's Syndrome*)

Scand J Rheumatology 1986; Suppl. 61: 26–27

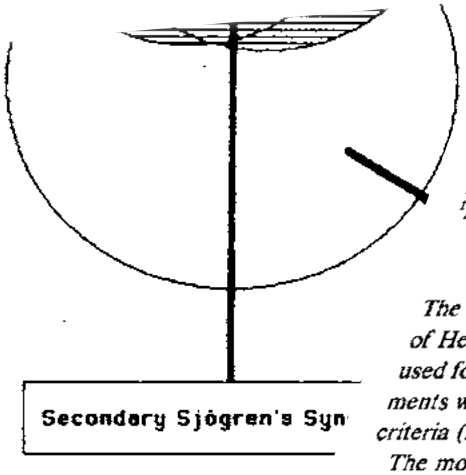

Fig. 1. Relationship between keratoconjunctivitis secondary Sjögren's Syndrome.

Criteria for Sjögren's Syndrom

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The criteria for Sjögren's syndrome was proposed by the of Health and Welfare of Japanese Government in 1977 (used for classification of patients with Sjögren's syndrom ments which provide the patients with medical aids. The criteria (2) and its translation is shown in Table I.

The modifications were made at four specific points fc

1. Addition of positive sialogram: this was added to de disease characteristic of Sjögren's syndrome without

Figure 4.6 *Examples of publications on criteria for Sjögren's syndrome.*

Diagnosis

4

Diagnostic criteria for a particular disease (so-called *target disease*) are needed if the target disease may be confused with other diseases (so-called *confusable diseases*) because of overlapping features.[12] For a diagnosis, the target disease has to be recognized in a pool of confusable diseases (figure 4.1).

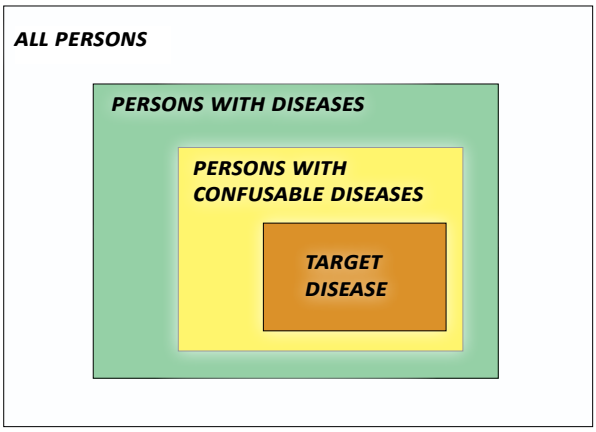

Figure 4.1 *Schematic representation of a target disease in a pool of confusable diseases from which it must be distinguished.*[12]

Theoretically, the target disease may be recognized in two ways: by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases as the cause of the symptoms (figure 4.2). Ideally, for the diagnosis of the target disease, both methods should be used because:

a. confusable diseases may be more common than the target disease; so if a confusable disease is present, recognition is mandatory as many can be treated;

b. failure to diagnose a confusable disease (unclassifiable confusable disease, unknown confusable disease or false-negative diagnosis of a confusable disease) would automatically incorrectly yield a diagnosis of the target disease;

c. patients may have a confusable disease *plus* the target disease.

If both methods are used, the diagnosis of the target disease is made on the basis of *exclusion* of confusable diseases and *confirmation* by the recognition of the presence of the specific combination of symptoms and signs of the target disease. If the main symptoms are not explained by a single diagnosis (confusable disease or target disease), a second diagnosis should be possible. This approach is useful in clinical practice as patients often have more than one disease. Recognition of confusable diseases is therefore considered to be an essential step in the diagnostic process.

In contrast to common belief, symptoms and signs for use in diagnostic criteria *do not need to be specific* for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the

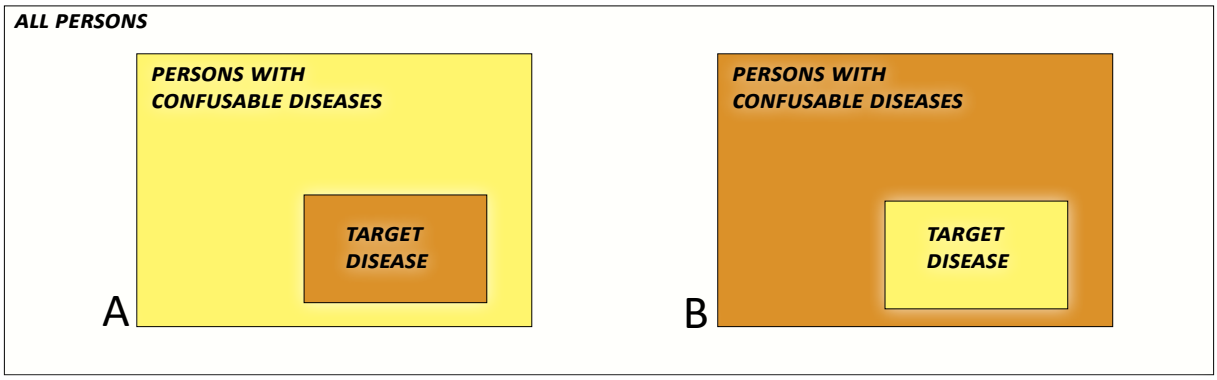

Figure 4.2 *Schematic representation by red areas of a diagnosis of the target disease by the recognition of the specific combination of features (A) or by exclusion of confusable diseases (B).*

Sensitivity and specificity

The terms sensitivity and specificity are often used to indicate the reliability of investigations and criteria.

Let us assume that we wish to establish disease B. The sensitivity is the proportion or percentage of the people with disease B who have an abnormal test or meet the criteria. The specificity is the proportion or percentage of the people without disease B who have a normal test or do not meet the criteria.

A problem with designing criteria is that some kind of method has to be found (the gold standard) that allows the disease to be definitely diagnosed or definitely excluded. The opinion of a group of experts is often used as the gold standard.

specific feature and diagnostic criteria would not be necessary. As is the case when individual people or music compositions are recognized, diseases can be recognized by their specific combination of features. For diseases, the combinations consist of the presence or absence of particular symptoms and signs and the results of a variety of clinical investigations.

Many diseases, particularly the generalized autoimmune diseases, can manifest the same symptoms. This can make it difficult to establish the right diagnosis. An important question concerns the basis on which the diagnosis is made. Criteria have been drawn up to ensure that diagnoses are made on the same basis. Criteria are mutual agreements about how the diagnosis is made.

There is a high level of consensus regarding the basic definition of Sjögren's syndrome: both the eyes and the mouth must be involved. However, many sets of criteria for Sjögren's syndrome have been published in the literature (figure 4.6).[1-11] There is more than one version of some of these sets. The sets differ with regard to the precise definition of what is considered abnormal, whether or not autoantibodies should be present and whether symptoms count.

Diagnosis for research

Where scientific research is concerned, it is essential for the diagnosis to be "absolutely" certain, even though patients who probably also have the disease are then excluded from research. After all, the main objective is to select only patients who definitely have the disease which is being studied. Some sets allow for possible or probable diagnosis. This is not in line with the purpose of the criteria which is to achieve a well-defined diagnosis for scientific research.

Generalized autoimmune diseases

In generalized autoimmune diseases, two or more organs are involved, in contrast with organ-specific autoimmune diseases where one organ is involved.

Diagnosis for clinical application

When diagnosing individual patients in the consulting room, every endeavour will be made to reach the most appropriate diagnosis. Signs and symptoms that are not specifically required for the final diagnosis are allowed to be taken into consideration. The main purpose here is to arrive at a usable diagnosis as a basis for treatment, check-ups and assessment of the prognosis.This means that if the research criteria are used to establish an individual diagnosis, patients sometimes do not fulfil the criteria, whereas on the basis of other criteria - including the exclusion of other diagnoses - they do in fact have Sjögren's syndrome.

Overlapping features of diseases

Figure 4.3 shows how disease B can be differentiated from diseases A and C. In situation 1 there is no overlap and disease B can easily be differentiated from diseases A and C. In situation 2 there are overlaps (indicated by *) and the decision has to be made as to whether patients with symptoms in these overlap areas *should* or *should not* be considered as having disease B.

When diagnosing individual patients (in the consulting room), situation 2a will be chosen. For the most definite diagnosis of B - for scientific research for instance - patients in the overlap area will not be considered as having disease B, even if it is quite probable that they do in fact have disease B.

Criteria are not definitive, but are continually being adapted in accordance with new insights and as new research data become available.

Research criteria are often used in clinical situations and clinical criteria are sometimes used for reseach purposes, and both situations are wrong. However, even the correct use of clinical criteria in clinical situations and of research criteria for research purposes, represents a continuous source of errors and misunderstanding. But even more important is that in all these situations, results from scientific studies cannot be extrapolated to patient populations. The ESSIC criteria for the diagnosis of interstitial cystitis/bladder pain syndrome is an example of how these problems can be avoided (see the chapter on Urogenital disorders, paragraph interstitial cystitis/ bladder pain syndrome).

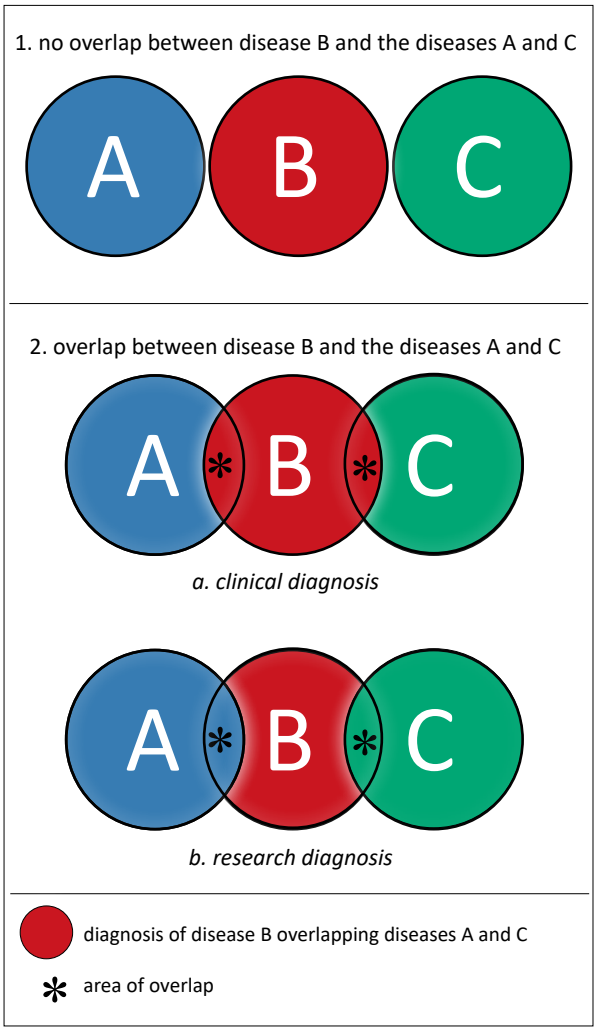

Figure 4.3 *In situation 1 there is no overlap between disease B and diseases A and C: disease B can easily be differentiated from diseases A and C without decision rules or criteria for the diagnosis. In situation 2, diseases A and C show an overlap with B and some kind of criteria are needed to diagnose disease B. When diagnosing individual patients in the consulting room, criteria are needed that allow the best fitting diagnosis (2a). For a diagnosis B that is most certain, for scientific research for instance, patients in the overlap area (*) will be excluded from the diagnosis B, despite it is quite possible that they do in fact have disease B (2b). The consequence of using separate sets of criteria for research purposes and clinical purposes is desastrous. See the chapter on incomplete Sjögren's syndrome for alternative ways to design criteria for both research and clinical applications.*

How to use diagnostic criteria?

In general, there is little point in carrying out the eye tests (item 3) in a patient who has no typical eye symptoms (item 1). Likewise, if a patient has no typical mouth or salivary gland symptoms (item 2), a lip biopsy (item 4) or other salivary gland test (item 5) is pointless.

In both situations the likelihood of finding abnormalities is minimal and not very relevant. There is likewise little point in continuing with investigations to diagnose Sjögren's syndrome if it is clear that the patient can no longer score 4 items. The reason for this is that it is only worth while carrying out diagnostic tests for Sjögren's syndrome if the probability exists of establishing a definite diagnosis (4 or more criteria items). If other possible causes have been excluded, characteristic symptoms give rise to the suspicion that it could be Sjögren's syndrome. Carrying out further investigations simply to get a stronger suspicion is of little value. It is more logical to wait *e.g.* a year before taking another look at whether the patient meets the criteria. In the meantime - if the suspicion of Sjögren's syndrome still exists - the patient should be treated in the same way as someone with a definite diagnosis.

The American-European criteria

For some years now, it has been the *European criteria* that have mainly been used to diagnose Sjögren's syndrome. These have been revised a number of times and the latest version was published in 2002, the so-called *American-European criteria*. They consist of 6 items (see table 4.1) that may be summarized as: ocular symptoms, oral symptoms, eye tests, lip biopsy, imaging or function investigation of the salivary glands and antibodies in the blood.

In general terms, Sjögren's syndrome can be diagnosed if 4 out of the 6 items are positive, see table 4.2 for details. A distinction is drawn between primary and secondary Sjögren's syndrome. The term secondary means that a second generalized autoimmune disease is present. The diagnosis of secondary Sjögren's syndrome can be established if only 3 of the 6 criteria items are present in addition to the other autoimmune disease.

The criteria are intended for scientific research. In comparison with other criteria, they have both advantages and disadvantages.

Advantages are that they are accepted worldwide, are flexible and can therefore also be used for clinical diagnosis. A disadvantage is they draw a distinction between primary and secondary Sjögren's syndrome. It would be more logical to apply one standard for the diagnosis of Sjögren's syndrome, regardless of any other concomitant diseases. A second disadvantage

Table 4.1 Revised international classification criteria for Sjögren's syndrome [10,11] **(so-called American-European criteria)**

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs-that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 minutes)
2. Rose bengal score or other ocular dye score (≥ 4 according to Van Bijsterveld's scoring system)

IV. Histopathology:
In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥ 1, defined as a number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Table 4.2 Revised rules for classification [10,11]

For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:
a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
b. The presence of any 3 of the 4 objective criteria items (that is: items III, IV, V, VI)
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS
In patients with a potentially associated disease (for instance another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria:
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

Explanation of symbols
< less than
≤ less than or equal to
> more than

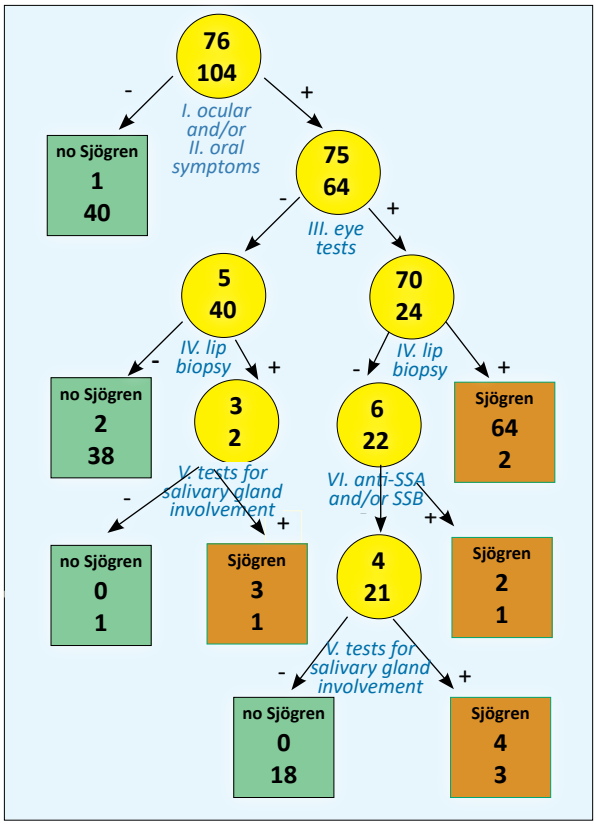

Figure 4.4 *Flow chart for the diagnosis of Sjögren's syndrome (classification tree method) with inform ation about false-negative and false-positive clas-sifications in the final situations according to the European criteria. The figures in the circles and boxes show the number of patients in the relevant node with Sjögren's syndrome (above) and "no Sjögren's" (below) respectively.*

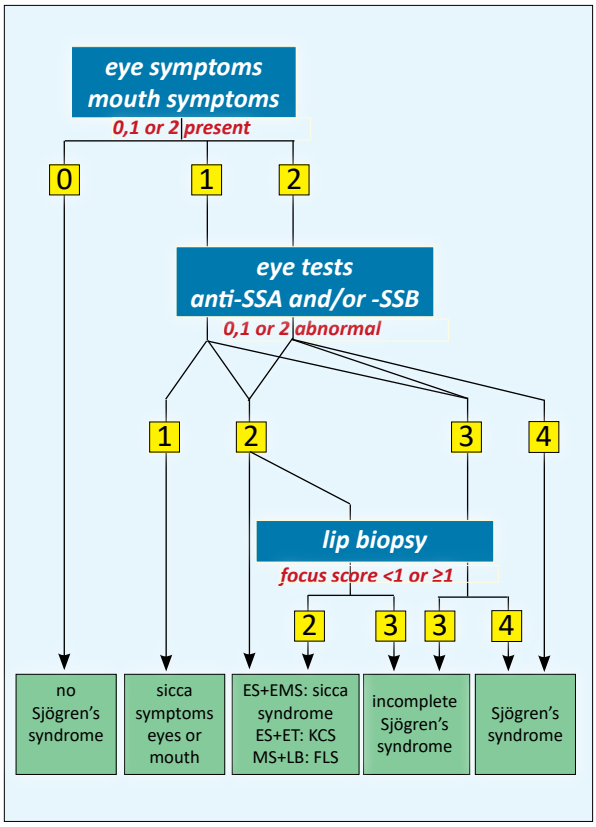

Figure 4.5 *Flow chart for the diagnosis of Sjögren's syndrome as used by the author. See text for further details. The yellow squares show the number of crite-ria items present.*
Abbreviations: ES: eye symptoms; MS: mouth symp-toms; ET: abnormal eye tests; LB: abnormal lip biopsy; KCS: keratoconjunctivitis sicca; FLS: focal lymphocytic sialoadenitis

is that a patient can fulfil the criteria even if both eye signs and eye symptoms are absent. If a patient has no ocular signs or symptoms, but does meet the criteria for salivary gland involvement, it would be better to call it focal lymphocytic sialoadenitis instead of Sjögren's syndrome. This would then be comparable with patients who only have ocular signs and symptoms and for years have been indisputably diagnosed as having keratoconjunctivitis sicca.

Abnormal biopsy .... may be normal !

15% of healthy subjects without complaints of dryness of the mouth or eyes have an abnormal lip biopsy with focus scores ranging from 2 to 6.

Radfar L et al (2002) [13]

Sequence of investigations

How should the criteria be applied in practice in order to make a diagnosis? There are no uniform rules for this. A logical method that is used by the author is described below.

It should first be established whether the eye and mouth symptoms are typical of Sjögren's syndrome (see table 4.1, items 1 and 2).

Blood tests [a] should be carried out to detect other possible causes of the symptoms and also for antibodies against SSA/Ro and SSB/La.

Eye tests should also be arranged (Schirmer test, break-up time and rose bengal dye test, see also chapter 13).

Once all the results are known, 2, 3 or 4 items of the criteria will have been fulfilled (see figure 4.5).

The diagnosis is complete if 4 items are present, if 3 are present a lip biopsy may be arranged as a focus score of at least 1 will give a definite diagnosis. If 2

Missed diagnoses .....

Almost 60% of patients diagnosed by experienced clinicians as Sjögren's syndrome do not fullfil the American-European criteria for Sjögren's syndrome.

Brun JG et al (2002) [14]

items are present, no further tests will be arranged because a definite diagnosis cannot be obtained.
Patients regularly have fewer than 4 items of the criteria. If other causes of the signs and symptoms have been excluded, Sjögren's syndrome may remain as the only probable explanation. Further treatment and check-ups should then be the same as in the case of people who fulfil all criteria.

Specificity of the lip biopsy
In 2002 a study was published on the findings in salivary gland biopsies of 54 healthy volunteers who had served as control subjects in various studies of salivary dysfunction.13 A biopsy with a focus score of more than 1 was regarded as positive (this is slightly different from the American-European criteria in which a focus score of 1 is also considered positive). The frequency of positive lip biopsies in the healthy subjects was 15%. The focus score ranged from 2 to 6 and none of the subjects had symptoms of dry mouth or dry eyes. The focus score showed no correlation with age, smoking, serologic findings or salivary flow in these subjects.

In a recent examination of inter-rater reliability for a group of 5 board-certified pathologists interpreting the same series of labial salivary gland biopsies, the agreement was found to be uniformly poor for judgments of diagnostic status, focus scores, and histological characteristics of biopsy specimens. This lack of reliability is troubling.[17]

Sensitivity of the European criteria to diagnose Sjögren's syndrome
Diagnostic criteria are usally designed for the purpose of scientific studies and, therefore, cut-off points are chosen to obtain a high specificity, a choice that invariably results in a lower sensitivity. Brun *et al.*[14] studied out-patients with a clinical diagnosis of Sjögren's syndrome of a rheumatology department of a Norwegian university hospital. They compared how many of these patients fullfilled the 1993 preliminary European criteria in comparison with the modified preliminary criteria [15] that are similar to the 2002 American-European criteria. The difference between these versions is that the modified and American-European criteria require a positive lip biopsy or the presence of antibodies to SSA/Ro and/or SSB/La, and that a positive ANA or rheumatoid factor is no longer part of the serology item. They found that of 203 patients with a clinical diagnosis of Sjögren's syndrome, 57.1% satisfied the preliminary criteria and only 40.9% the modified (and thus also the American-European) criteria. Ramos-Casals *et al* [24] found that only 45% of Sjögren's patients according to the 1993 criteria fulfilled the 2002 criteria.

The advantage of application of the modified and American-European criteria is that this results in more homogeneous and comparable patient populations in research. The disadvantage is that up to 60% of patients who could be diagnosed by experienced clinicians as Sjögren's syndrome, do not get a diagnosis anymore, and no proper treatment in many cases. This is the reason that we proposed previously to use the name Sjögren's like syndrome in patients who fullfil 3 items of the criteria and in whom no other explanation of the symptoms and signs can be found.[16] This terminology is in line with the one used for patients with the antiphospholipid syndrome and 3 of the items of the diagnostic criteria for SLE (antiphospholipid syndrome with lupus-like syndrome). A better term, however, probably is *incomplete Sjögren's syndrome* as the word "like" suggests that it only looks the same but is in reality different. See also the chapter on incomplete Sjögren's syndrome.

Noninvasive techniques to detect salivary gland changes
Diagnostic methods to detect changes in the salivary glands include gland biopsies and x-ray sialography. These invasive methods may cause substantial complications for the patient. Noninvasive techniques such as ultrasonography (US) and magnetic resonance imaging (MRI) have been used to reliably characterize and diagnose Sjögren's syndrome and offer promise as replacements for the earlier invasive and potentially harmful techniques.

MRI sialography
Tonami et al evaluated the effectiveness of MRI sialography of the parotid gland ducts in the diagnosis and staging of Sjögren syndrome.[18] In control subjects, the main duct and the primary branching ducts of the parotid glands were clearly visible on MRI sialographic images. In patients with Sjögren syndrome, a punctate, globular, cavitary, or destructive appearance was well seen within the parotid glands. Findings obtained at

[a] For practical reasons, blood tests are simultaneously carried out to check for abnormalities that are important to assess the severity of the Sjögren's syndrome.

MRI sialography correlated well with the results of labial gland biopsy.

Tonami concludes that MRI sialography has the potential to produce diagnostic findings in the parotid gland ducts of patients with Sjögren syn drome and speculates that this method will augment and possibly replace x-ray sialography.

Roberts *et al* used dynamic contrast-enhanced MR imaging and tracer kinetic modeling to quantify the microvascular pathophysiologic features of Sjögren's syndrome.[19] They found considerable heterogeneity in microvascular changes in the parotid gland in patients with Sjögren's syndrome. The results demonstrate that dynamic MR tracer kinetic modeling parameters can enable quantification of the parotid gland microvascular characteristics related to the pathophysiologic features seen with Sjögren's syndrome.

Ultrasonography

El Miedany *et al* assessed the diagnostic value of parotid gland quantitative assessment using US as well as MRI in patients with Sjogren's syndrome and to evaluate the possibility of using such modalities as a predictor of the histopathologic score of salivary gland biopsy in this group of patients.[20] Patients and control subjects were scored according to the structural changes seen in both radiologic modalities. In addition, sialography and labial gland biopsy were done for all patients as well as the control subjects and scored according to the degree of affection.

Parenchymal inhomogenity (PIH) was seen in 93.6% of the patients studied by US, while nodular pattern was seen in 97.8% in the MRI study. The US and MRI results correlated significantly with the histopathologic score of the minor salivary glands (r =0.82, 0.84, respectively) as well as sialography score (r = 0.69, 0.60, respectively). There was good agreement between US and MRI findings (r = 0.87) in both SS cases and control subjects. The authors conclude that US and MRI are equally sensitive tools for the diagnosis of salivary involvement in patients with Sjögren's syndrome. Quantitative assessment of US and MRI images seem to represent an advance in the diagnosis of Sjögren's syndrome as they offer a good prediction of the pathology score of the salivary gland. MRI seems unnecessary as a routine diagnostic tool and should be considered as the second option in case of normal US.

Wernicke *et al* verified US criteria for examination of the major salivary glands in diagnosis of primary and secondary Sjögren's syndrome.[21] They selected 316 consecutive patients: 57 had primary Sjögren's syndrome, 33 secondary Sjögren syndrome, 78 sicca symptoms, and 148 patients served as asymptomatic controls. Evident parenchymal inhomogenicity in 2 or more major salivary glands was detected by US in patients with primary and secondary Sjögren's syndrome with a sensitivity of 63.1% and 63.6%, respectively. The specificity of this imaging approach was 98.7%. The volume of submandibular glands was reduced in patients with primary and secondary SS by about 30% compared to patients with sicca symptoms and asymptomatic controls. In patients with primary Sjögren's syndrome, parenchymal inhomogenicity of the salivary glands was strongly associated with positivity for anti-SSA/Ro and/or anti-SSB/La antibodies. The authors conclude that US detection of parenchymal inhomogenicity of the major salivary glands and observation of reduced volume of the submandibular glands resulted in high specificities for diagnosis of primary and secondary Sjögren's syndrome.

Salaffi *et al* compared US of salivary glands with contrast sialography and scintigraphy, in order to evaluate the diagnostic value in primary Sjögren's syndrome.[23] US arose as the best performer, followed by sialography and by salivary gland scintigraphy.

Obinata *et al* [25] examined the reliability and correlation of sialography, salivary gland biopsy, and US for Sjögren syndrome and evaluated the usefulness of US as a diagnostic tool [26] for Sjögren syndrome

Table 4.3 Grading of ultrasonography [26]

Grade	*Findings*
0 (homogeneity)	Normal glands
1 (slight inhomogeneity)	Small hypoechoic spots
2 (mild inhomogeneity)	Multiple scattered hypoechoic areas (2 mm)
3 (evident inhomogeneity)	Multiple hypoechoic areas (2-6 mm)
4 (gross inhomogeneity)	Multiple hypoechoic areas (6 mm)

Ultrasonography

... the replacement of older imaging techniques with ultrasonography - a simple, inexpensive, and non-invasive diagnostic tool that does not expose patients to radiation - is certainly feasible and desirable.

Tzioufas AG, Moutsopoulos HM (2008) [22]

Ultrasonography arose as the best performer, followed by sialography and by salivary gland scintigraphy.

Salaffi F et al (2008) [23]

compared with sialography and histopathology. Seventy-three patients who underwent sialography, US, and salivary gland biopsy were included in this study. They found a statistically significant difference in the sensitivities of sialography and histopathology, in the specificities of sialography and US, and in the accuracies of sialography and both US and histopathology. The authors conclude that ultra-sonography can be used as a diagnostic tool for Sjögren's syndrome, with its advantage of noninvasiveness and ease of use.

From these studies it may be concluded that ultrasonography - a simple, inexpensive, and non-invasive diagnostic tool that does not expose patients to radiation - seems an excellent replacement of older imaging techniques as well as lip biopsies for the diagnosis of Sjögren's syndrome. Lip biopsies, however, remain important to differentiate Sjögren's syndrome from confusable diseases such as sarcoidosis and malignant lymphomas in selected patients.

The American-European criteria critically reviewed

The criteria and rules as described in tables 4.1 and 4.2 are in contradiction with the approach given in figure 4.4 from the same paper in which a patient is classified as "no Sjögren" if typical mouth and eye complaints are absent.

It is remarkable and - in my opinion - an omission that the objective finding of one or two enlarged parotid glands at physical examination is not an (objective) item of the criteria. It counts as part of subjective item II when the patient confirms recurrent of persistent swollen salivary glands as an adult, but this item is already positive when the patient has the daily feeling of a dry mouth for more than three months. The physical finding of enlarged parotid(s) has a different meaning as compared to the symptoms of diminished function of the salivary gland and should score separately.

Sub-item II.1 (feeling of a dry mouth) is very common and nonspecific while the majority of Sjögren's patients fullfils sub-item II.3. Therefore, II.1 can better be removed. But item II.3 is inappropriate as it refers to the *habit* of drinking during meals. It could better be replaced by the question "Do you *need* to drink liquids to be able to swallow dry food?". The need to drink to make swallowing food possibe is probably an excellent physiological test for the saliva production of the parotid glands. Further studies should be done to see whether the salivary flow measurement (item V.1) has additional diagnostic value in this case, which I doubt.

Item V contains both expressions of diminished salivary gland function (sub-items V.1 and V.3) as well as anatomical abnormalities such as ductiectasia.

Autoantibodies to SSA/Ro and SSB/La occur independently and are associated via autoimmune diseases such as Sjögren's syndrome and subacute cutaneous lupus erythematodes. The probability that a patient suffers from Sjögren's syndrome is much higher if autoantibodies are found to both SSA/Ro and SSB/La as compared to only one of them. Unfortunately, for the diagnostic criteria having antibodies to both SSA and SSB has no more weight than the presence of antibodies to only one of them.

In the author's opinion, items for criteria should be clustered within five groups:

1. *symptoms* of dry mucous membranes as reported by the patient
2. objective evidence of *diminished function* of exocrine glands
3. objective evidence of abnormal *macroscopic* exocrine glands
4. objective evidence of abnormal *microscopic* exocrine glands
5. *autoantibodies*

Group 1: Symptoms
- typical eye symptoms
- typical mouth symptoms

Group 2: Diminished gland function
- abnormal Schirmer test
- diminished salivary flow
- abnormal scintigraphy

Group 3: Abnormal macroscopic anatomy
- parotid gland enlargement at physical examination
- abnormal findings at ultrasonography
- abnormal findings at sialography

Group 4: Abnormal microscopic anatomy
- abnormal focus scores as detected in tear glands or any salivary gland

Group 5: Autoantibodies
- autoantibodies to SSA (52kD)
- autoantibodies to SSA (60 kD)
- autoantibodies to SSB
- rheumatoid factor with negative anti-CCP
- a positive ANA with no evidence of SLE (?)

The weight for the diagnosis of each of these items should be determined with the aid of approprate

statistical analysis.

This should be followed by typing of the disease to garantee that all patients who have Sjögren's syndrome according to expert opinions, as well as patients with incomplete Sjögren's syndrome, can be classified as Sjögren's syndrome with the addition of a particular type. Typing of various subgroups of diseases has been shown to be a successful approach in finding optimal treatments for various malignancies. See also the chapter on urogenital disorders, paragraph on interstitial cystitis/bladder pain syndrome, for an example of diagnostic criteria with typing of the disease

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*
04.02.2010	information added from refs 24 and 25
04.02.2010	grading of ultrasonography added (table 4.3; ref 26)
04.02.2010	fig 4.3 added; various text changes and additions
09.02.2010	legend fig 4.3: text changed
30.03.2010	changes in the paragraph on The American-European criteria critically reviewed

Treatment

5

A diagnosis of Sjögren's syndrome does not automatically mean that treatment is necessary. Once a diagnosis of Sjögren's syndrome has been made, an assessment is necessary of any damage and what developments may be expected in the future.

The possibility and need for treatment depend on the signs, symptoms and risks of the disease. Possibilities for treating Sjögren's syndrome are not different to those for other generalized autoimmune diseases. Due to the wide variation in signs and symptoms, treatment may greatly differ per patient, while considerable individual variations are also seen in the effect of medication on the patient. Sjögren's patients have an increased risk of allergic reactions to drugs.[1,2]

After the assessment, the following scenarios for treatment are possible:

a. treatment is necessary for medical reasons

b. the patient wishes to have treatment for a specific symptom

c. treatment is neither necessary nor desired.

The advantage of this approach is that it is clear why treatment is being given, how the result is evaluated and whether the treatment should be continued or stopped after a specific period of time. Indications for treatment can be subdivided into inflammation, dryness and other indications.

Has the desired effect of a drug been obtained?

When a drug is being taken, it is important to assess after a period of time whether the desired effect has been achieved.

Laboratory tests can be used to evaluate objective signs of the disease, such as inflammation.

Assessment of the effect of a drug on symptoms is dependent on the patient's own impression.

If after a period of time no improvement is seen in signs or symptoms, there is no point in continuing with the drug in question. When assessing symptoms and signs, account should be taken of their natural course.

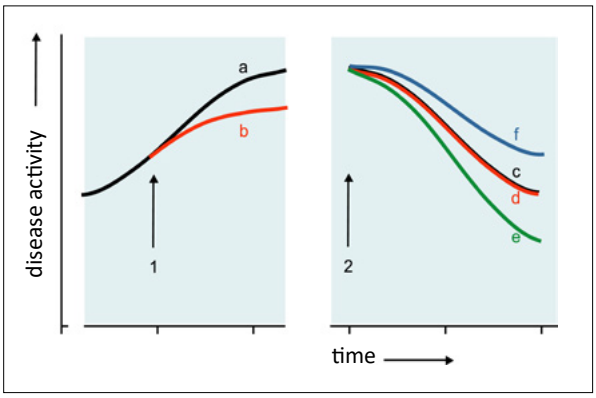

Figure 5.1 *The assessment after a period of time of the effect of a drug can be very difficult if the complaints have a fluctuating course (see text).*

This is difficult if the signs or symptoms are subject to remissions and relapses and consequently very variable. This is explained in figure 5.1. Let us assume that a symptom has a natural course as shown by line a. If a treatment is started at time 1 and the sign or symptom improves as shown by line b, the drug has an unmistakeably positive effect, but despite this the sign or symptom has become worse.

Suppose that the sign or symptom has a natural course as shown by line c. A treatment is started at time 2. Here, the sign or symptom decreases in all cases, for example if the drug has no effect (d), a positive effect (e) or even a negative effect (f).

The conclusion is therefore that a longer period of time is usually necessary to assess whether a drug has had a positive effect. A critical approach and common sense help accurate assessment of any effect.

This chapter on treatment is divided into a section on treatment of symptoms and signs and a section on specific drugs.

A. TREATMENT FOR SPECIFIC SYMPTOMS OR SIGNS

This section is divided in treatment of dryness, inflammation and for disease manifestations that cannot be classified as dryness or inflammation.

TREATMENT OF DRYNESS

Sjögren's syndrome is first and foremost an exocrinopathy, an abnormality of exocrine glands (glands that secrete moisture). This may cause severe symptoms. By definition this concerns the eyes and mouth, but the dryness may also occur in other organs such as the nose, bronchial tubes, vagina, skin and intestines.

In some organs symptoms of dryness can be treated locally, *e.g.* the eyes (artificial tears), the mouth (artificial saliva), the nose (ointment) and the skin (cream). Local treatment may be sufficiently effective, particularly in the case of mild symptoms.

Disadvantages, however, are that they only have a local effect and are not really an adequate replacement for your own tears, saliva etc.

Systemic treatment (use of medication for a general effect, *e.g.* by taking tablets) is gaining increasing importance in the treatment of dryness. Advantages are that it stimulates the formation of your own moisture, including the protective substances they contain, and that it is often effective in more than one part of the body. Disadvantages are that these are drugs that may have side-effects and are not effective and/or suitable for everyone. The main drugs used for systemic treatment are pilocarpine [3-5] (see paragraph on pilocarpine) and cevimeline [6,7] (not obtainable in Europe). Positive effects can also be seen from bromhexine 3x 8-16 mg/day,[8-10] N-acetylcysteine 3x 200 mg/day [11] or nizatidine 300 mg/day.[128,129] If required, pilocarpine can be combined with each of them. Treatment with pilocarpine and nizatide will be discussed further.

In a prospective, randomized, double-masked trial, omega-3 was *not* found to be better than wheat germ oil in stimulating saliva production.[166]

Local treatments of dryness

Local treatment of dry eyes

In many patients, eye irritation can be improved with artificial tears, preferably no more than 4-6x a day. If the result is unsatisfactory, it may be worthwhile trying another brand (see also chapter 20, question 45).

Some people are unable to tolerate certain preservatives that are added to bottles of artificial tears. It is then worth trying artificial tears containing a different preservative or trying preservative-free artificial tears. These are often supplied in single use containers or a special bottle which can be used for up to three months once opened.

Local treatment of dry mouth

Artificial saliva products, such as Xialine® and Saliva orthana®, are available for local treatment of the mouth. Glandosane® is a watery artificial saliva that is effective for a short period of time. Oral Balance® is a gel that is mainly suitable at night. The effect of these treatments depends on the correct usage, so read the instructions for use carefully.

A disadvantage is that artificial saliva cannot be used for eating problems. Dryness of the mouth can cause gumline caries around the neck of a tooth. It is important to discuss the use of *e.g.* fluoride tablets and/or application of fluoride with your dentist and have frequent check-ups, for example every 3 months.

Local treatment of dry nose

Symptoms caused by dry mucous membranes in the nose can be treated locally using physiological salt. If there is crust formation in the nostrils, an ointment containing 10% Emser salt in *oculentum simplex* or Nisita® nose ointment can be used. You can make physiological salt (0.9%) yourself by dissolving 9 grams of kitchen salt (NaCl) in 1 litre of water. Place a little of this solution in the palm of your hand and sniff it hard up into your nostrils. You should spit out any water that runs down into your throat. Do this several times consecutively and repeat it a couple of times a day.

Local treatment of dry skin

Many patients with Sjögren's syndrome have a dry skin. Showering should be short and the water not too hot. After showering, smear your skin while still wet with 20% *vaselinum album* in *cremor lanette I.* Allow this to sink into your skin for a few minutes before dressing.

Local treatment of dry vagina

Dryness of the mucous membranes of the vagina can have different causes, such as the menopause, but is also a well-known symptom of Sjögren's syndrome.

Treatment with pilocarpine (see further) improves (symptoms of) vaginal dryness in about one-third of women. Lubricants (*e.g.* Sensilube®, KY Jelly®) can be used if required. The following alternative can be made up on prescription by the pharmacy:

hypromellose	3 gr
glycerol 85%	50 gr
methylparabene 15% FNA	1 ml
water to make a total of	100 ml

TREATMENT OF INFLAMMATION

Inflammation in Sjögren's syndrome is caused by the infiltration of organs by mainly $CD4^+$ T lymphocytes. These organs are the lacrimal glands (resulting in keratoconjunctivitis sicca) and the salivary glands (focal lymphocytic sialoadenitis). Similar inflammation may occur in the bronchial tubes (*bronchitis sicca*), lungs (*lymphocytic interstitial pneumonia*), kidney tubules (*interstitial nephritis*), stomach (*autoimmune gastritis*) and liver (*autoimmune hepatitis* and *primary biliary cirrhosis*). Inflammation may also occur in the small blood vessels (*leukocytoclastic vasculitis*) and joints (*arthritis*). Vasculitis can damage organs due to impaired blood circulation.

Inflammation should be treated if it is likely to cause damage to an organ. If this is only expected in the longer term, the patient can be treated with hydroxychloroquine (HCQ), usually 400 mg/day for 3 months, followed by 200 mg/day (see also section on HCQ). If there is a risk of organ damage in the short term, temporary treatment with corticosteroids may be necessary, preferably in combination with HCQ. After a few months, the treatment with corticosteroids can be stopped again. In the case of inflammation that is unlikely to lead to damage but which nevertheless requires treatment of the symptoms it causes, NSAIDs (prostaglandin synthesis inhibitors) can be used for a period of time. The principle behind treatment with HCQ, corticosteroids and NSAIDs is explained in figure 5.2 (see text accompanying the figure).

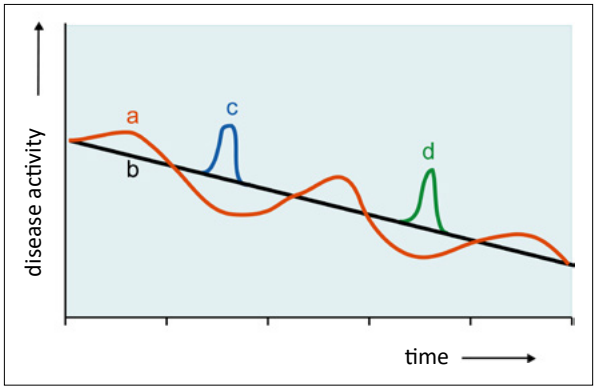

Figure 5.2 *Graph illustrating the principle of treating inflammatory conditions with hydroxychloroquine, corticosteroids and NSAIDs. The red line* **A** *shows the variable course of the disease activity over a number of years and line* **B** *the average disease activity. The purpose of hydroxychloroquine is to (gradually) reduce the disease activity as illustrated by the downward trend of lines* **A** *and* **B** *over the years. Non-dangerous flare-ups of the disease (***C***) can be successfully treated with NSAIDs on a temporary basis. Dangerous flare-ups (***D***) should be treated with short courses of corticosteroids.*

Disease activity and disease damage

The course of many autoimmune diseases is characterized by periods of disease inactivity and disease activity (flares). Flares show variable resolutions or persist resulting in damage to the affected organ. It is very important to distuinguish disease activity from damage as activity may be reversible while damage may be permanent (irreversible). See chapter 17 for further information.

Inflammation of the tear glands and ocular surface

Tear glands

Inflammation of the lacrimal glands does not usually necessitate separate treatment. If required, the above-mentioned agents can be used.

Ocular surface

If the surface of the eyes is inflamed, treatment with the usual artificial tears can be supplemented by eye-drops containing an anti-inflammatory agent such as cyclosporine A 0.05% (Restasis®) 2-4 times a day or corticosteroid, or with autologous serum.[161,163] Topical corticosteroid is effective in achieving rapid resolution of acute inflammation, whereas topical cyclosporin A would be safer for long-term maintenance. These anti-inflammatory therapies provided subjective improvement in dry eye symptoms in 70% of patients.[161]

Eye drops containing vitamin A as retinyl palmitate have been found to be equally effective as cyclosporin A 0.05% in patients with dry eye syndrome.[162] *Note:* dry eye syndrome is a general term for various disorders attributable to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort.[162]

Vitamin A

Vitamin A is essential for maintaining the health of epithelial cells. Vitamin A deficiency adversely affects these cells in the eyelid, conjunctiva, and cornea. Vitamin A can exist in 3 forms: retinol, retinal, and retinoic acid. Many tissues requiring vitamin A store the vitamin as an ester of retinal. Retinyl palmitate (an ester of retinol and palmitate) is found in cells of the lacrimal gland and retinol is found in the tears. Its presence in tears provides the rationale for treating dry eye disease with vitamin A.[162]

Inflammation of the mouth

Infection with *Candida albicans* can cause a burning, red tongue and cracks in the corners of the mouth.[12-14] Topical treatment is possible with amphotericin B (Fungizone®) in many patients as long as some saliva is produced. Systemic treatment with tablets often works better than local treatment, for example 200 mg fluconazole for 15-30 days. If the fungal infection returns after this, treatment with *e.g.* 50 mg fluconazole a day may be necessary for 3 months. Another agent can also be tried, for example itraconazole, 2x 100 mg/day for 30 days. Sometimes the fungal infection is resistant to both of these agents. If this is the case, a combination of 200 mg fluconazole and 250 mg terbinafine for 14 days is often a solution.[15]

If symptoms recur, treatment with fluconazole 150 mg once a week may be effective in preventing symptomatic oral candidiasis (see also reference 76). Take a new toothbrush and disinfect any dentures.

In a study in which patients with Sjögren's syndrome were treated with 3x 5 mg/day pilocarpine, at the start of the study 75% of the patients were found to be infected with *Candida albicans*. After a year's treatment, this percentage had fallen to 25%.[16]

Inflammation of the salivary glands

About a third of patients with Sjögren's syndrome experience unilateral or bilateral swelling of the large salivary glands.[17,18]

The swelling may sometimes be bothersome or painful and require treatment. It should be borne in mind that infections, stones and malignancies can sometimes be a cause of swelling. If this is not the case, good results can be achieved by using HCQ with pilocarpine and/or bromhexine.[19,20]

In rare cases, a short treatment (*e.g.* 1-2 weeks) with corticosteroids can be beneficial. If the swelling forms a constant and/or recurrent problem and if there is an increased risk of a non-Hodgkin lymphoma (high sedimentation rate, antibodies to SSA/Ro and/or SSB/La, monoclonal or oligoclonal abnormalities), it may be necessary to remove the salivary gland surgically (see also the chapter on surgery and anaesthesiaor for special precautions to be taken in the case of operations).

Acute parotid swelling

Acute parotid swelling is usually due to bacterial infection of the parotid gland and a common complication in patients with Sjögren's syndrome. It may be effectively treated with 500 mg of levofloxacine once daily for 30 days.

Acute bacterial infection of the parotid gland, a common complication in patients with Sjögren's syndrome, may be effectively treated with 500 mg of levofloxacine once daily for 30 days.

Inflammation of muscles and joints

When considering whether to start treatment for arthritis, it should be remembered that joints are virtually never damaged by Sjögren's syndrome alone. If a second autoimmune disease is present, it should be investigated whether the arthritis is related to this. Generally speaking, arthritis resulting from rheumatoid arthritis will be treated to prevent damage to the joints.

Muscle inflammation (myositis) is relatively rare and mild forms either require no treatment or can be treated with hydroxychloroquine.[21] The indication for treating inflammation of joints and muscles in Sjögren's syndrome is therefore mainly the accompanying pain (see under: Pain in muscles and joints).

Inflammation of the lungs

The branches of the windpipe, the bronchi or bronchial tubes, may become inflamed due to dryness. This is known as *bronchitis sicca* [22-24] and can be improved by the use of pilocarpine with or without bromhexine or acetylcysteine.

The lungs may contain lymphocytic infiltrates, comparable with those found in the salivary and lacrimal glands.[25,26] This condition is known as *lymphocytic interstitial pneumonia* for which treatment with prednisolone is usually necessary, sometimes with the addition of azathioprine. Mild forms sometimes respond well to HCQ. Active forms of this inflammatory condition sometimes lead to a non-Hodgkin lymphoma in the lungs.[27-30] Pulmonay disorders in Sjögren's syndrome are discussed in a separate chapter.

Inflammation of the skin

Skin complaints caused by exposure to sunlight can often be treated with HCQ 200 mg/day.[31,32] However, HCQ can sometimes make the skin more sensitive to sunburn and invariably exacerbates pre-existing or subclinical psoriasis.[33-39]

Inflammation of blood vessels (vasculitis)

Vasculitis (inflammation of the blood vessels) occurs in a quarter of patients with Sjögren's syndrome, usually in the form of hypersensitivity vasculitis (leukocytoclastic vasculitis) with for example hives (urticaria) or purpura (dot-like bleeding into the skin), particularly on the lower legs. In rare instances, medium-sized blood vessels (arteries) are involved in the process. As in other complications, the need for

treatment and the method to be used depends on the degree or risk of organ damage. This treatment can vary from prostaglandin synthesis inhibitors (NSAIDs), non-NSAIDS (*e.g.* HCQ, colchicine, diaphenylsulfone (Dapsone®) to corticosteroids and drugs such as azathioprine. An even more aggressive therapy, *e.g.* cyclophosphamide, may be necessary in the case of vasculitis of the central nervous system or in polyarteritis nodosa forms of arteritis (inflammation of medium-sized arteries).

Inflammation of the kidneys

At least three different kidney disorders may occur in Sjögren's syndrome.[40-42]

Interstitial nephritis (inflammation of the renal tubules) may diminish the kidney function in some patients. Treatment is given then with prednisolone. If the kidney function (creatinine clearance) is normal, treatment may only be necessary for any associated acidosis, hypokalaemia (low potassium in the blood) or hyperventilation.

Glomerulonephritis (kidney filter inflammation) is rare in Sjögren's syndrome, in contrast with systemic lupus erythematosus (SLE). Treatment with corticosteroids and *e.g.* azathioprine, cyclophosphamide or a mycophenolate is usually necessary.

A third kidney problem can occur as a manifestation of the *antiphospholipid syndrome (APS)*, when small clots or thrombi occur in the blood vessels causing insufficient blood flow to the kidney.[43] Treatment consists of anticoagulation.

Nonbacterial inflammation of the urinary bladder

Interstitial cystitis (bladder pain syndrome) is a nonbacterial inflammatory condition of the urinary bladder. It was recently found that interstitial cystitis is not uncommonly associated with either Sjögren's syndrome or individual components such as keratoconjunctivitis sicca or focal lymphocytic sialoadenitis. For further information see the chapter on urogenital disorders.

VARIOUS DISORDERS

Some features of Sjögren's syndrome cannot be classified as inflammation or dryness. These include: thrombocytopenia, antiphospholipid syndrome, hypergammaglobulinaemia, cryoglobulinaemia and Raynaud phenomenon. Treatment corresponds to that for the isolated forms and for other autoimmune diseases. They are briefly discussed below.

Thrombopenia and antiphospholipid syndrome

Thrombopenia (low platelet count) occurs in about 11% of patients with Sjögren's syndrome and only needs treating in the case of (a risk of) haemorrhaging. In the first instance this consists of a high dose of corticosteroids. If necessary, gammaglobulins (IgG) can also be administered intravenously. If this proves inadequate, removal of the spleen may be considered. A new approach is the anti-B cell therapy with *e.g.* rituximab (see further). Severe autoimmune thrombopenia rarely occurs with Sjögren's syndrome and may be a reason to suspect SLE.

Thrombopenia may also be associated with antiphospholipid antibodies in APS. APS may also manifest itself in the form of recurrent thrombosis in veins or arteries (lung embolism, cerebral thrombosis, aseptic bone necrosis) and repeated miscarriage. This form of thrombopenia may respond well to salicylates (aspirin), *e.g.* between 38 and 120 mg calcium carbasalate a day, although this treatment cannot be started in a period when there is a strong tendency to bleed.[44]

Raynaud phenomenon

Raynaud phenomenon occurs in about one third of patients with Sjögren's syndrome.[17,45-47] It is important to test for cryoglobulinaemia (see box) or other causes of increased viscosity (stickiness) of the blood (such as a greatly increased IgM level) that need to be treated separately (see chapter 14).

It is essential to keep the whole body warm, including the (fore)head. Smoking is strictly advised against. Drugs can sometimes lead to an improvement, with the possibility of treatment in the winter only. A *Cochrane* review showed that calcium channel antagonists (*e.g.* sustained-release nifedipine 2-3x 10-60 mg/day) were the only group of drugs with proven efficacy in Raynaud phenomenon.[140] The treatment sometimes has to be stopped due to headache or low blood pressure. Other possible drugs that are used but with less well documented efficacy are ketanserin (1-3x 20-40 mg/day) and fluoxetine (20 mg/day).[48-51]

If ulcers develop on the hands or feet, 38-100 mg/day calcium carbasalate may help to speed healing and prevent new ulcers.

Sympathectomy (cutting through specific nerves) is not recommended for Raynaud phenomenon.

Raynaud phenomenon: treatment

When treating Raynaud phenomenon, it is essential to keep the whole body warm, including the (fore)head. Smoking is strictly advised against.

Cryoglobulins

Cryoglobulins are complexes of mainly antibodies that form a gel at low temperatures and can consequently make the blood 'thicker'. They mainly occur in malignant blood diseases, autoimmune diseases (especially Sjögren's syndrome) and in infection with the hepatitis B or hepatitis C virus. Cryoglobulin*aemia* means the occurrence of cryoglobulins in the blood.

Hypergammaglobulinaemia and cryoglobulinaemia

In some patients, the concentration of the serum immunoglobulins (antibodies) is increased (hypergammaglobulinaemia).

Greatly increased concentrations of IgG and IgM, with or without cryoglobulins, can cause vasculitis and hyperviscosity (blood is too thick and sticky). If tests show that the IgG and/or IgM levels are continually increasing, it is useful to start early treatment with HCQ. This will allow the levels to stabilize and then decrease. If problems already exist due to high concentrations of immunoglobulins, treatment may be necessary with corticosteroids and immunosuppressive agents. This also applies to severe forms of cryoglobulinaemia (see chapter on clinical investigations).

SUBJECTIVE INDICATIONS FOR TREATMENT

Patients often have symptoms for which there is no medical need for treatment. If these symptoms have a very detrimental impact on the patient's quality of life, the advantages of treatment may be greater than the disadvantages. This may be the case for example with (debilitating) fatigue and severe muscle and joint pain, with or without objective signs of inflammation.

Fatigue

Fatigue is an important, frequently occurring symptom in Sjögren's syndrome and often forms a particularly debilitating aspect of the disease for the patient. It can come on quite suddenly and greatly vary per day. Since fatigue cannot be seen and is difficult to assess objectively, it often causes major problems for the patient at work and within the family.

Furthermore, medical examining authorities often have little or no conception of fatigue as such. See the chapter on fatigue.

It is first necessary to investigate whether there is any specific identifiable cause of the fatigue, either in relation to the Sjögren's syndrome or some other cause. If a cause is found, this can often be treated successfully and the fatigue may subside.

If inflammation in the joints, muscles or blood vessels is the cause of the fatigue, anti-inflammatory agents such as HCQ, NSAIDs and prednisolone can be used for treatment. Prednisolone has, not without reason, acquired a somewhat tarnished reputation among both doctors and patients. However, one should be aware of "throwing out the baby with the bath water". Provided that there is a good reason for it, low doses of prednisolone taken for several weeks and preferably on alternate days can some times lead to a substantial improvement without giving rise to side effects. If necessary, this can be repeated several times a year.

If sleep disturbance due to insufficient sleep at night is the cause of the fatigue, this should be treated by trying to eliminate the cause. This might be pain or anxiety, for example.

Depression is a common cause of tiredness. However, the drugs used to treat this often exacer bate the dryness symptoms of the mouth and eyes.

If a patient has DRTA (distal renal tubular acidosis), referred to earlier, potassium citrate, *e.g.* 3x per day 0.5 to 2 grams, can help to restore the acidity level and to correct the lower than normal serum potassium. It is very important for the potassium level in the blood to be regularly checked since potassium levels that are too high are dangerous. If there is no need to correct the potassium level, sodium citrate or magnesium citrate can be used as well in equivalent dosages.

If the magnesium in the red blood cells is too low, magnesium gluconate helps (3x two capsules of 250 mg). These forms of treatment are safe provided they take place under medical supervision.

If the fatigue is severe, it may be worth considering trying to improve it with certain drug*s (e.g.* HCQ or rituximab). This is only justifiable if the balance between the possible side effects of the drug and the result that can be expected is favourable.

A small double blind placebo-controlled study has shown that two infusions of rituximab 1 gr (with oral and intravenous steroids to avoid serum sickness) significantly improvement fatigue and social functioning six months later.[92] See further for more information on rituximab.

If treatment is not possible or unsuccessful, the only possibility that remains is to adapt one's life style. A few rules of thumb may help here:

- get up on time because lying in bed too long can exacerbate the fatigue (maintain a normal day and night rhythm)
- divide up your day, start by doing something for a couple of hours and then rest for about 20 minutes
- you may need 3 to 4 rest breaks during the day

- avoid stress peaks by spreading activities throughout the day and week
- try to prioritize by using your energy on activities that you yourself find important and not on what you feel others expect you to do (be a bit "egoistic").

Pain in muscles and joints

If treatment is required for pain in the muscles and joints, the first choice after paracetamol (acetaminophen) would be HCQ, followed by prostaglandin synthesis inhibitors (preferably the lowest effective dose of selective cox-2 inhibitors such as celecoxib or etoricoxib, see further). The same applies to inflammation of muscles and joints (see above), but paracetamol will only have a pain relieving effect.

The preference for HCQ is connected with the relatively infrequent occurrence of side effects and the fact that it is often an effective treatment for more than one problem.

HCQ can be effective for skin disorders caused by sunlight (increased sensitivity to sunlight is a rare side effect), for treating signs and symptoms of leukocytoclastic vasculitis in the skin, for (poly)myositis, it reduces the risk of thrombosis by antiphospholipid antibodies and lowers a high IgG level. The results achieved from treating joint and muscle pain differ greatly per patient and per drug.

Depression

Depression is not uncommon in Sjögren's syndrome. The depression may be a reaction to having the disease and is often of a temporary nature.

Fatigue (especially fatigue that is present first thing in the morning and improves during the course of the day), difficulty concentrating, forgetfulness, poor appetite and sleep disturbances may be symptoms of depression. Bearing in mind that vasculitis, particularly of the small blood vessels, can cause neuropsychiatric symptoms, it is worthwhile treating any existing vasculitis (see above) if there are indications that the depression could have an organic cause. Tests should also be carried out to check for antiphospholipid antibodies in the blood because these can cause thrombosis, including in small blood vessels in the brain. Recurrent minor damage can eventually lead to severe disorders.

If the depression has no organic cause, help is needed from a psychotherapist. When treating, it is important to use modern antidepressants without an anticholinergic side effect that might otherwise considerably exacerbate the symptoms of dryness. The term "anticholinergic side effect" means that the drug inhibits certain functions of the nervous system, causing increased dryness of the mucous membranes.

B. SYSTEMIC TREATMENT WITH SPECIFIC DRUGS OR GROUPS OF DRUGS

In this section, some drugs that are commonly used for treatment of various aspects of Sjögren's syndrome are discussed.

Against dryness
- pilocarpine
- bromhexine
- acetylcysteine
- nizatidine

Against pain
- paracetamol (acetaminophen)
- tramadol
- opiates

Against inflammation
- nonsteroidal antiinflammatory drugs (NSAIDs)
- corticosteroids
- colchicine
- dapsone (diaminodiphenylsulfone)

Immunomodulating antiinflammatory drugs
- hydroxychloroquine
- azathioprine
- methotrexate
- cyclosporin
- mycophenolate mofetil
- cyclophosphamide

TNF-targeted biologicals
- infliximab
- etanercept
- adalimumab

IL-6 targeted biologicals
- tocilizumab or atlizumab

Anti-B lymphocyte biologicals
- rituximab
- epratuzimab
- belimumab

Anti-T lymphocyte biologicals
- abatacept
- efalizumab
- alefacept

Pilocarpine

The purpose of treatment with pilocarpine is to stimulate the salivary and lacrimal glands into making more saliva and tear fluid. Other exocrine (moisture secreting) glands sometimes also function better such as those in the nose, ears, Eustachian tube, oesophagus and other parts of the intes tines, skin and vagina. The effect starts half an hour after taking the dose and lasts 3-5 hours (see figure 5.3).

Pilocarpine improves the production of saliva and tears, resulting in better protection of mucous membranes. It can be prescribed as capsules or as tablets. The starting dose is usually 4x 5 mg/day. The patient can choose when to take the dose, but taking it half an hour before meals can improve eating. The effect may improve after a few months.

Common side effects of the drug include flushing, sweating and more frequent urination than usual. The patient can decide whether to continue despite the side effects, or whether it is preferable to stop.

7.5% of people over the age of 65 years experience mild symptoms of dizziness. The pupil may become smaller. This can be a disadvantage for some people because it can make seeing in the dark more difficult, which is particularly important when driving a car.

Depending on the drug's effect and any side effects, the dose can be adjusted. In the case of "normal" body weight, the maximum dose is 10 mg 4x per day. This dose can be tried if the effect of the standard dose of 5 mg 4x per day is insufficient and there are no bothersome side effects. Instead of 4x 10 mg, it is also possible to take 8x 5 mg or if necessary 16x 2.5 mg: the advantage of taking a lower dose more frequently is that you avoid high peaks of pilocarpine in the blood. This is especially important if bothersome sweating occurs as a side effect half an hour after taking the pilocarpine. If no improvement is seen within a few months even with the higher dose, the pilocarpine treatment can be immediately stopped. It is also possible to take pilocarpine as and when needed.

Pilocarpine can be taken in combination with other medicines. However, in the case of betablockers (mainly used to treat heart disease, and for high blood pressure in the past), it is advisable to start with a low dose because the combination may cause heart conduction disorders. If a patient benefits from taking pilocarpine, it can be used on a long-term basis. Studies show that oral symptoms improve in about 60% of patients and eye symptoms in almost half of the patients.

Pilocarpine comes from a plant, the *Pilocarpus jaborandi.* It acts through binding to the M3 muscarinic receptor on gland cells as normally occurs with

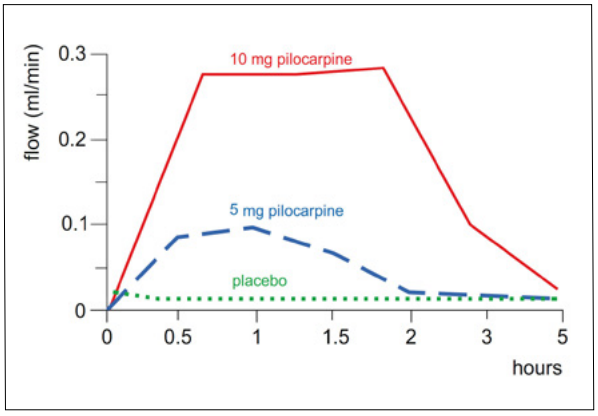

Figure 5.3 *Pilocarpine effect on unstimulated parotid saliva flow. Note that doubling the dose triples the saliva output (MGI Study P89-05).*

acetylcholine (see chapter on cause). Recent research has shown that acetylcholine does not bind successfully to M3 receptors in patients with Sjögren's syndrome because there are antibodies to the M3 receptor that block this. The effective action of pilocarpine in 60% of patients with Sjögren's syndrome, *irrespective of the duration of the disease* (!), indicates that the diminished function of the glands is not only the consequence of damage to the glands but is above all due to the reduced possibility of acetylcholine reaching the M3 receptor. It is conceivable that the inflam mation of the glands may be the consequence of the M3 antibodies binding to the M3 receptor. If this is indeed the case, treatment with pilocarpine should in the long term also have a positive effect on the inflammation. In the future we are likely to see more M3 receptor agonists appearing on the market with longer lasting and more specific binding to the M3 receptor, for example cevimeline.

Local pilocarpine and cevimeline

Eyes

Pilocarpine eye drops are used to treat increased eye pressure (glaucoma). These drops should not be used for the treatment of dry eyes in Sjögren's syndrome because they do not help this condition and can worsen eye disorders. Nor should the drops be drunk in a glass of water. The amount of pilocarpine that is swallowed in this way can greatly vary.

Mouth

A randomized-controlled trial published in 2002,[134] tested a pilocarpine mouthwash formulation, used orally for 1 minute in healthy individuals. Increased objective salivary flow persisted for 75 minutes for both 1% and 2% pilocarpine without significant side

Oxford levels of evidence and grades of recommendation

level	*type of evidence*
1a	meta-analysis of randomised trials
1b	at least one randomised trial
2a	one well-designed controlled study without randomisation
2b	one other type of well-designed quasi-experimental study
3	non-experimental study (comparative study, correlation study, case reports)
4	expert committee, expert opinion

grade	*nature of recommendation based on*
A	clinical studies of good quality and consistency including at least one randomised trial
B	well-conducted clinical studies without randomised trials
C	absence of directly applicable clinical studies of good quality

effects. The subjective sensation of increased salivary flow was measured by visual analogue scale (VAS) and was improved in subjects using the 2% dose. This new formulation may allow the use of pilocarpine locally, thus minimizing side effects.

The efficacy of gargling 3x a day before meals using 30 mg cevimeline dissolved in 100 ml of water for each session, was tested in healthy subjects and patients with Sjögren's syndrome.[136] Cevimeline gargle markedly increased salivary flow rates in 2 of 5 patients. In the remaining 3, the effect was negligable. In 3 of the 5 patients clinical symptoms improved subjectively. No adverse effects were seen. These preliminary data indicate that further studies are warranted with local oral treatment with pilocarpine and cevimeline. *However, a 2% pilocarpine solution contains 20 mg of pilocarpine per ml mouthwash and the swallowing of 1 ml of the mouth wash is a overdose.*

Level of evidence for the efficacy of systemic pilocarpine

Two randomized-controlled trials in the Sjögren's syndrome literature met the highest level of evidence.[131,132] In both studies, pilocarpine 5 mg given orally 3x or 4x daily demonstrated a significant increase in saliva output rate and improved subjective measures. Pilocarpine given orally was safe and effective in improving symptoms of oral dryness in patients with mild to severe hyposalivation. The duration of the increased salivary flow was 2-3 hours.[131]

Pilocarpine has been approved in several countries, but not all, for the treatment of radiationinduced or Sjögren's syndrome-induced xerostomia. Based on strong evidence,[130-132] the use of pilocarpine for these conditions is recommended.[133] The recommended dose is 5 mg orally 3x a day with titration up to 10 mg.[135] Classification of Recommendation class I, Level of Evidence A (see box).

Bromhexine and ambroxol

Bromhexine (Bisolvon®) is a mucolytic agent used in the treatment of respiratory disorders (*e.g.* cough with phlegm) associated with viscid or excessive mucus. Bromhexine reduces mucus viscosity by splitting disulfide bonds linking proteins in the mucus.

Clinical studies have shown that it increases the quantity of bronchial secretion and reduces its viscosity due to depolymerization of the mucopolysaccharide fibres in mucus. The maximum effect is reached after some days. Reported side-effects have been harmless and infrequent. Ambroxol is a pharmacologically active metabolite of bromhexine and used for the same indications.

In a double-blind randomized placebo-controlled trial bromhexine 16 mg 3x a day has been found to significantly improve the Schirmer test and tear break-up time in patients with Sjögren's syndrome.[137,138]

N-acetylcysteine

N-acetylcysteine is a drug used mainly as a mucolytic agent and in the management of paracetamol (acetaminophen) overdose.

N-acetylcysteine acts through its free sulfhydryl group which opens up the disulfide bonds in the mucoproteins thus lowering mucous viscosity.

Twenty-six patients with primary or secondary Sjögren's syndrome were treated in a double-blind, cross-over trial for a four week period with oral n-acetylcysteine and placebo.[139] Sjögren's syndrome patients reported statistically significant improvements in ocular soreness, ocular irritability, halitosis and daytime thirst. N-acetylcysteine, but not placebo improved the van Bijsterveld score, but no effect was seen on the Schirmer test, the tear break up time or any of the laboratory tests.

Nizatidine

The H_2 receptor antagonist nizatidine (Axid®) inhibits acetylcholinesterase, resulting in an increased availability of acetylcholine, and was recently shown to stimulate salivary secretion in healthy volunteers.[128] In a small randomized trial, 27 patients with Sjögren's syndrome were assigned to receive nizatidine (n=14, 300 mg/day) or another H2 blocker, famotidine (n=13, 40 mg/day; control) and followed for eight weeks.[129]

Assessments of oral dryness were done using a visual analog scale (VAS; 1-100 mm) and the Saxon's test, respectively. Patients receiving oral nizatidine, but not famotidine, obtained significant objective relief from their xerostomia and mild subjective improvement.

Paracetamol (acetaminophen)

Paracetamol (acetaminophen) is a widely-used analgesic and antipyretic drug. Paracetamol lacks many of the side-effects of NSAIDs. It has no antiinflammatory effects. Paracetamol-related liver disease is an important public health problem that is usually related to taking more than 4 g of paracetamol per day. [155]

Acute overdoses of paracetamol can cause potentially fatal liver damage and, in rare individuals, a normal dose can do the same.

There are no specific data on the use of paracetamol in Sjögren's syndrome.

Tramadol

Tramadol is a centrally acting analgesic for treatment of moderate to severe pain including neuralgias. It acts on an opioid receptor as well as the noradrenergic and serotonergic systems. It is often combined with paracetamol.

Side effects may be nausea, vomiting, sweating, drowsiness and constipation. In patients with epilepsy and in others by overdosing, it may cause seizures.

There is no literature on its use in Sjögren's syndrome.

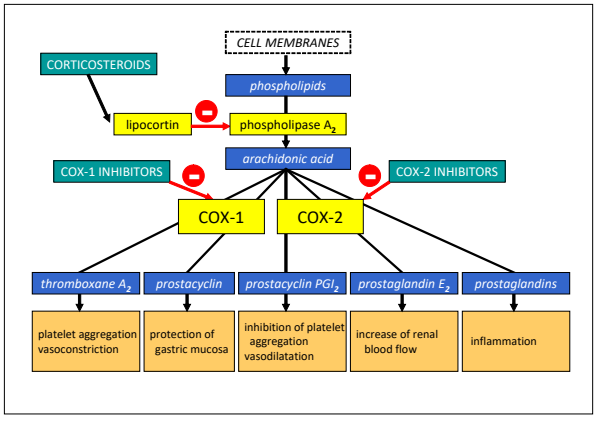

Figure 5.4 *Chart showing the effects of NSAIDs on cyclo-oxygenase-1 and 2 (cox-1 and cox-2 respectively) and corticosteroids on phospholipase A_2.*

Table 5.1 Examples of effects on cox-1 and cox-2 of prostaglandin synthesis inhibitors

	inhibition of	
cox-1 + cox-2	***cox2 > cox1***	***selective cox-2***
acetylsalicylic acid	diclofenac	celecoxib
azapropazon	meloxicam	etoricoxib
calcium carbasalate	nabumeton	lumiracoxib
ibuprofen		parecoxib
ketoprofen		rofecoxib [a]
indomethacine		valdecoxib [a]
naproxen		
piroxicam		
sulindac		
tenoxicam		
tiaprophenic acid		

[a] rofecoxib and valdecoxib were withdrawn from the market in 2004-05 due to an increased risk of cardiovascular events (including heart attack and stroke)

Opiates

Opiates are a group of drugs, such as morphine, heroin and codeine, that contain or are derived from opium. Opiates are prescribed for relief of (severe) pain but the mode of action is poorly understood.

Certain patients may require 10 times the dose to get the same level of pain relief as others. Side effects such as nausea or sedation can be debilitating to some and nonexistent for others.

Common adverse effects include euphoria, itching, nausea, vomiting, drowsiness, dry mouth, miosis, orthostatic hypotension, urinary retention and constipation.

The addiction potential also varies among people. Groups at particular risk are chronic pain patients, health care providers and drug abusers.

There is no literature on the use of opiates in Sjögren's syndrome but side effects such as dry mouth and constipation may limit their use.

Non-steroidal anti-inflammatory drugs (NSAIDs)

There are various groups of anti-inflammatory drugs such as corticosteroids (*e.g.* prednisolone), prostaglandin synthesis inhibitors and others (*e.g.* HCQ and colchicine).

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the inflammation by inhibiting cyclooxygen-

The NSAID problem

NSAIDs are used on a massive scale and many are available over-the-counter. In the United States, it is estimated that they cause 16,500 deaths annually from gastrointestinal bleeding. [63] In the case of the Netherlands, this would represent around 800 deaths a year due to the use of NSAIDs.

In recent years, NSAIDs that selectively inhibit cox-2 (coxibs) have become available such as rofecoxib, celecoxib, etoricoxib, lumiracoxib and valdecoxib. Rofecoxib and valdecoxib have now been withdrawn due to cardiovascular side-effects (strokes, myocardial infarction). However, the same cardiovascular side-effects have also been found for the older NSAIDs with the possible exception of naproxen.

Preliminary NDA (New Drug Application) data of the FDA (www.fda.com) suggest that the death rate per 100 patient years is for: placebo 0, etoricoxib 0.24, non-naproxen NSAIDs 0.36 and naproxen 0.17.

ase-2 (cox-2) and are therefore called prostaglandin synthesis inhibitors. Until recently, all NSAIDs on the market also inhibited cyclo oxygenase-1 (cox-1). Table 5.1 shows NSAIDs classified according to inhibition of cox-1 and/or cox-2.[74,75]

Cox-2

When tissue damage occurs, arachidonic acid is formed from phospholipids of the membrane of white blood cells with help of phospholipase A_2. With the help of cox-2, this in turn forms prosta glandins (PGs). These PGs cause inflammation and symptoms such as pain, fever and vasodilation (figure 5.4).

Cox-1

Prior tissue damage is not necessary for the production of cox-1. Cox-1 is continually being formed and not especially by white blood cells. Cox-1 is needed, for example, for the production of PGs that protect the gastric mucosa (lining of the stomach) and for the production of thromboxane A_2 (TxA_2) that stimulates the aggregation of platelets and causes constriction of blood vessels.

NSAIDs that also inhibit cox-1 consequently may cause damage to the gastric mucosa while hemostasis (blood stanching) is affected in all users. This unfortunate combination of effects may cause gastric mucosa bleeding. This risk is reduced if a proton pump inhibitor (*e.g.* omeprazole) that inhibits the formation of gastric acid or miso prostol (restores the prosta glandin effect on the gastric mucosa) is also taken.

Selective cox-2 inhibitors (coxibs)

Due to the absence of the cox-1 effect, the risk of gastric adverse effects is smaller and the function of the platelets is not affected. This results in a lower risk of gastrointestinal complaints, perforations, ulcers and bleeding.[64-71] The risk of gastro intestinal events caused by coxibs is somewhat less than half the risk of old NSAIDS.

Inhibition of cox-2 has been found to increase the risk of cardiovascular thrombotic events such as heart attack and stroke. This is due to the inhibition of the prostacyclin PGI_2 (figure 5.4). PGI_2 is a natural inhibitor of aggregation of platelets and induces dilatation of blood vessels. In healthy subjects, the prothrombotic effect of TxA_2 is counter acted by the antithrombotic effect of PGI_2.

Coxibs and low-dose aspirin

In the treatment of cardiovascular disease, inhibition of the function of platelets (a cox-1 effect) is often desirable. If necessary, the selective cox-2 inhibitors can be combined with low dose aspirin, unlike ibuprofen and indomethacin that render low dose aspirin ineffective.[73] However, cardiovascular disease is a contraindication for the use of all NSAIDs with the possible exception of naproxen.

The balance between effects of Txa_2 and PGI_2

Old NSAIDs reduce both TxA_2 and PGI_2, and the equilibrium between the opposite effects is therefore more or less sustained.[72] This is probably true for patients with no systemic inflammatory disease such as osteoarthritis, but may be not true for patients with rheumatoid arthritis, for example.

Low-dose aspirin (40-100 mg/day) only blocks the formation of TxA_2 and is therefore antithrombotic. Coxibs inhibit PGI_2 in a dose-dependent way and have a pro thrombotic effect in susceptible persons. However, recent data suggest that the old NSAIDs (with the possible exception of naproxen) have similar cardiovascular adverse effects.[77]

Other adverse effects

The coxibs unfortunately have the same adverse effects as the old NSAIDs in the form of a possible rise in blood pressure, impairment of the kidney function in the case of a pre-existing kidney disorder, fluid retention, congestive heart failure and constipation.

Other favourable effects

Usually, a high level of COX-2 expression is found in cancer cells. Protective effects of NSAIDs including aspirin and coxibs, have been found on the prevention and treatment of cancers.[172] Examples include: nonmelanoma skin cancers [169], breast cancer [170], and colorectal cancer.[171]

Several double-blind, randomized, placebo controlled studies suggest that celecoxib is an effective adjuvant agent in the management of patients with major depression. [167,168]

Conclusion

If the use of painkillers/anti-inflammatory drugs is necessary, a choice has to be made between one from the old NSAIDs or one from the new coxibs. For patients with previous gastric ulcers, perforation or bleeding, a coxib is the first choice. This also applies to patients on anticoagulant therapy. For patients with ischemic vascular disease (thrombosis, heart attack, stroke) or with risk factors, it may be safer to combine naproxen and a proton pump inhibitor such as omeprazol. This may also apply to healthy women on oral contraceptives.

However, the results of ongoing (*e.g.* EDGE, EDGE II, MEDAL)[77] and new studies are necessary before final conclusions can be drawn with regard to the cardiovascular safety of preparations.

Corticosteroids

Corticosteroids are synthetic forms of cortisol, a hormone made by the adrenal glands. Well-known examples are prednisone, prednisolone, dexamethasone and hydrocortison.

High doses of corticosteroids (*e.g.* prednisolon) should only be considered in life-threatening or otherwise severe irreversible complications. The risks of side-effects such as osteoporosis, high blood pressure (hypertension), diabetes mellitus, muscle weakness, cataract, glaucoma, puffy face, thin skin and infections, have to be accepted under these circumstances, but can sometimes be reduced by certain measures. Increased bone resorption due to prednisolone can be counteracted by *e.g.* alendronate 1x a week one tablet of 70 mg or etidronate/calcium carbonate.

Colchicine

Colchicine inhibits neutrophil and monocyte chemotaxis, collagen synthesis and mast cell histamine release. It is mainly used for gout for about 2600 years now. More recent applications are Behçet's disease, familial mediteranean fever, psoriasis, vasculitis, systemic sclerosis including CREST syndrome, sarcoidosis, idiopathic pulmonary fibrosis[144] and recurrent aphthous stomatitis.

Never combine colchicine and clarithromycin

The FDA noted 117 nonoverdose[1] deaths (some recent) that were associated with oral colchicine (with 51% involving an interaction between colchicine and clarithromycin).[165]

Woodcock J, Okada S
Food and Drug Administration
Silver Spring, MD [165]

[1] 4.8 mg over 6 hours for acute gout is not considered to be an overdose; compare this dose to the low dose used for autoimmune diseases of 0.5 mg 1-3x a day.
[2] clarithromycin is often use as one of the drugs in the triple therapy for eradication of *Helicobacter pylori* in the stomach

Gastrointestinal side affects are common but are usually harmless and dose dependent. Other side effects are astonishing absent.[141] Although uncommon, colchicine poisoning may cause severe systemic effects. For acute gout high doses have been used: the FDA noted 117 nonoverdose deaths (some recent) that were associated with oral colchicine (with 51% involving an interaction between colchicine and clarithromycin).[165] Clinical trials of colchicine showed that lower doses were as effective as higher doses (4.8 mg over 6 hours)and produced fewer side effects. Toxic doses produce, in addition to nausea and vomiting, bone marrow suppression often leading to sepsis, hypocalcemia, adult respiratory distress syndrome, and direct cardiotoxic effects.[143,149]

In Sjögren's syndrome colchine may be used for hypergammaglobulinemic purpura,[142] other forms of vasculitis and arthritis. A common and safe dosage is 0.5 mg, 1-3x a day. Liver enzymes should be tested after three months

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone precursor produced from cholesterol by the adrenal glands and several other organs. It is the precursor of androstenedione, which can undergo conversion to testosterone and the oestrogens oestrone and oestradiol.

Low levels of serum DHEA have been found in SLE, RA and Sjögren's syndrome. It was subsequently

hypothesized that normalizing DHEA levels could be beneficial. There is some evidence that this may be true in SLE but randomized double-blind placebo-controlled trials showed no evidence of efficacy in Sjögren's syndrome.[146,147] Moreover, Pillemer *et al* [146] warn against the use of unregulated DHEA supplements, since long-term adverse consequences of exposure to this hormone is unknown.

Dapsone (diaminodiphenylsulfone)

Dapsone (diaminodiphenylsulfone, DDS) is available as a drug since the 1940s and continues to be a powerful drug in many skin diseases including leprosy.[151]

As an anti-infective agent, it is also used for treating malaria and for *Pneumocystic jiroveci* (carinii) pneumonia in AIDS patients. Dapsone has been found to be uniquely effective against a number of non-infectious inflammatory diseases, of which dermatitis herpetiformis (a skin diseased related to celiac disease) is the best known. The response of this disease to the drug is so dramatic (the pruritus is relieved within 48-72h) that it has even been considered as being a diagnostic indicator.

Dapsone acts against bacteria and protozoa in the same way as sulphonamides. Dapsone also inhibits the release and function of neutrophil lysosomal enzymes but the antiinflammatory action is not fully understood.

Dapsone in Sjögren's syndrome

No clinical studies are available on the use of dapsone in Sjögren's syndrome. Case reports and the use of dapsone for clinical features that may also occur in Sjögren's syndrome, warrant the use of dapsone in selected cases of Sjögren's syndrome when first choice therapies failed or were contraindicated.

Examples are idiopathic thrombocytopenic purpura, urticarial vasculitis and leukocytoclastic vasculitis.[151-153]

Contraindications and monitoring of patients

Dapsone is used by millions of patients without serious problems. Rare but potentially harmful adverse effects necessitate careful monitoring of patients under this treatment. Dapsone is considered unsafe in the following conditions: severe anemia, porphyria, deficiency of glucose-6-phosphate dehydrogenase, glutathione reductase or methemoglobin reductase, allergy to sulfonamides, or significant liver disease. It should not be paired with other hemolytics or dideoxyinosine. Before starting therapy, a complete blood count, reticulocyte count, glucose-6-phosphate dehydrogenase level, liver function studies, urinanalysis and renal function tests should be performed. During therapy, complete blood count, reticulocyte count, platelet count and leukocyte count with differential should be obtained weekly for the first month, then twice per month during the next two months and every three months thereafter. Liver and renal function should be tested every three months.

Methemoglobin levels should be obtained in patients who become symptomatic (see below) for methemoglobinemia.[151]

Adverse effects

Long-term administration of dapsone at standard doses (100 mg/d) usually results in methemoglobinemia of 15%. Methemoglobin is a form of hemoglobin in which the iron in the heme group is Fe^{3+} and not Fe^{2+} as in normal hemoglobin. Methemoglobin, however, cannot carry oxygen. Normally 1-2% of people's hemoglobin is methemoglobin. Methemoglobin levels <20% are not usually associated with symptoms. Dyspnea, nausea and tachycardia usually occur at levels of 30% or above, while lethargy, stupor and deteriorating consciousness occur as methemoglobin levels approach 55%. Levels of 70% are usually fatal. Agranulocytosis is, unlike methemoglobinemia, a severe idiosyncratic reaction. Idiosyncratic drug reactions are rare, unpredictable and dose-independent drug reactions. The probable mechanism is a complex immune-mediated cytotoxicity. For unknown reasons, the risk of agranulocytosis in patients with dermatitis herpetiformis is more than 25-fold (1 of 240-425) compared with other patients, whereas this side effect in patients with leprosy is almost unknown.[151]

Another serious idiosyncratic adverse effect is the *dapsone-induced hypersensitivity syndrome*. The unpredictability and potential severity of this reaction make it a major concern in clinical practice. Although this reaction to dapsone is rare considering the widespread use of the drug, it ranks high among drugs that cause this syndrome. Dapsone-induced hypersensitivity syndrome usually appears four or more weeks after initiation of therapy. Symptoms include a mononucleosis-like rash with fever and lymphadenopathy. Involvement of other organs varies and includes the liver (hepatomegaly, icterus, hepatitis and hepatic encephalopathy), lymphadenopathy, eosinophilia, and others. The course of the disease is also variable, but it may last four weeks or more and fatalities have been reported.

Exanthematous skin eruptions usually resolve within two weeks of stopping dapsone, although patients in whom Stevens-Johnson syndrome or toxic epidermal necrolysis develops have increased morbidity and mortality.

Hydroxychloroquine

Hydroxychloroquine (Plaquenil®) and chloroquine (Nivaquin®) are among the safest drugs with anti-inflammatory and disease-modifying properties. These effects are not exerted through inhibition of cox-1 or cox-2 (see further).[104] It often takes 2-6 months before an improvement can be seen.

Although we are talking here about hydroxychloroquine (HCQ), chloroquine has similar but not identical effects and side effects: 3.0 mg chloroquine is equivalent to 6.5 mg HCQ. Hydroxychloroquine has less side-effect than chloroquine (see next pages).

Hydroxychloroquine (Plaquenil®)

- the elimination half-life is about 40 days; this results from extensive tissue uptake and slow redistribution back into the blood from large tissue repositories
- it is widely distributed throughout the body, accumulating in blood cells, kidney, liver, lung and eye
- it is partially converted to de-ethylated metabolites in the liver and is eliminated principally via the kidneys
- it also forms an ether glucuronide that is excreted in the bile; about 25% is excreted renally unchanged

Effects

Disease-modifying means that the drug has a positive effect on the course of the disease and that it does not simply suppress symptoms. In addition to its original use for the treatment and prevention of malaria, it has been successfully used for around 50 years for the long term treatment of various chronic conditions such as rheumatoid arthritis and forms of lupus erythematosus (LE) such as discoid LE, subacute cutaneous LE and systemic LE.[52,53]

More recently, it has been used to treat diseases such as Sjögren's syndrome, sarcoidosis, polymyositis (inflammatory muscle disease), vasculitis, porphyria cutanea tarda, cutaneous manifestations of dermatomyositis, asthma,[107] hyperlipidemias and thromboembolic prophylaxis for patients with antiphospholipid antibodies.[31,52-61]

All drugs have in addition to the desired effects adverse side-effects. Hydroxychloroquine, however, also has several unexpected *favourable* side-effects (see table 5.2).

Table 5.2 Favourable effects of hydroxychloroquine (HCQ) other than anti-inflammatory and disease-modifying

- HCQ has a *lipid lowering* effect even if the patient takes corticosteroids [109-111]
- it directly reduces the binding of antiphospholipid antibody β_2-glycoprotein I complexes to phospholipid bilayers; [94] this may be one of the explanations of the *antithrombotic effects* of HCQ in patients with the antiphospholipid syndrome
- it *prevents vitamin D deficiency* in SLE patients [95]
- among SLE patients, steroid treatment is associated with the highest degree of vascular damage, and HCQ is associated with the *lowest degree of vascular damage* [98]
- HCQ treatment is associated with *later onset of SLE* in people with autoantibodies [99]
- HCQ has a *protective effect on survival of SLE patients* which is evident even after taking into consideration the factors associated with treatment decisions [100]
- SLE patients on antimalarials (mainly HCQ) have a *6-7x decreased risk for various cancers* [112]
- HCQ *improves glucose metabolism and insulin sensitivity* among patients with SLE [115-116]
- it *reduces the risk of infection* in hospitalized patients with rheumatoid arthritis (RA) [96]
- RA patients using HCQ have a reduced (62% of normal risk; 23% after 4 years) risk of diabetes [117]
- the prevalence of *aged-related macular degeneration (AMD)* in RA cases is about 10-fold lower than in general populations of similar racial origin; this is attributed to the use of antiinflammatory drugs including HCQ[118]
- it is efficious to *treat severe granulomatous complications* in a patient with CGD (chronic granulomatous disease) [97]
- HCQ has *antihyperglycaemic properties* in patients with type 2 diabetes mellitus [115]
- and do not forget: it is an *antimalarial* too

Table 5.3 Possible adverse effects of hydroxychloroquine treatment (see text for further information and references)

- hypersensitivity reactions (rash, fever)
- increased sensitivity to sunburn
- pigment changes
- reversible diffuse hair loss
- exacerbation of (subclinical) psoriasis
- temporary blurred vision
- exacerbation of subclinical myasthenia gravis
- maculopathy (preventable)
- myopathy (rare)
- cardiomyopathy (very rare; partially reversible)
- alterations in hearing (very rare)

HCQ in Sjögren's syndrome

There is only one double-blind placebo-controlled study on HCQ treatment in Sjögren's syndrome. This two-year cross-over trial in 19 patients from two centers was done by Kruize *et al* [93] The only effect that was found was an improvement of hyperglobulinaemia, ESR (erythrocyte sedimentation rate) and IgM.

In a retrospective study of 50 Sjögren's patients, Fox *et al* [58] found the following effects of HCQ:

- sustained improvement of local symptoms (painful eyes, painful mouth)
- improvement of systemic manifestations (arthralgias and myalgias) after treatment
- a significant improvement in ESR and IgG levels

In an open-label study of HCQ, Tishler *et al* [106] saw a significant reduction of some salivary inflammatory markers at the end of 12 months as well as partial clinical effects.

Inflammatory conditions in Sjögren's syndrome that can be treated with HCQ are those of the salivary glands, muscles, joints, blood vessels and nerves. Laboratory abnormalities such as increased ESR, anaemia and increased serum IgG can show improvement. HCQ also reduces the risk of thrombosis caused by antiphospholipid antibodies, can lower cholesterol levels and probably reduces the risk of a non-Hodgkin lymphoma and other malignancies.

Symptoms for which a trial treatment would be worthwhile include severe joint and muscle pain, recurrent flu-like feeling or fever and fatigue.

In addition to its use for inflammatory conditions, HCQ can also sometimes be used for symptoms without objectively determinable abnormalities.

Hydroxychloroquine and heart conduction

Hydroxychloroquine, in contrast to chloroquine, has not found to be associated with heart conduction disorders.

Costedoat-Chalumeau et al (2007) [101]

Side effects

Side effects are relatively mild and uncommon. They mainly concern allergic reactions (red rash, fever), increased sensitivity to sunburn, pigment changes in the skin or hair loss that recovers after stopping treatment (see table 5.3).

Exacerbation or manifestation of (subclinical) disease

Psoriasis

Psoriasis is often exacerbated but not an absolute contra-indication.

Myasthenia gravis

A rare side effect of HCQ is double vision and/or (increase in) muscle weakness. This may be an indication of a hitherto undiagnosed mild form of myasthenia gravis and should be reported to the specialist (see also chapters 2, 7 and 13).

Heart

Conduction disorders

A high incidence of heart conduction disorders, including bundle-branch block and incomplete or complete atrioventricular block, has been observed among patients treated with chloroquine. HCQ, however, has not found to be associated with heart conduction disorders.[101]

Cardiomyopathy

An extremely rare but possibly fatal side effect of HCQ is *cardiomyopathy*. Thirteen cases have been described to date.[119] Several diseases that are treated with HCQ can cause cardiomyopathy themselves. Examples are myocarditis, vasculitis, SLE, systemic sclerosis. HCQ-associated cardiomyopathy is characterized by myocyte vacuolization at light microscopy and both myelin figures and curvilinear bodies on electron microscopy.[119] Recently, a 64-year-old women with SLE was described, treated for more than 10 years with prednisone and HCQ, who presented with severe progressive dyspnea on exertion.[156] Endomyocardial biopsy revealed sarcoplasmic clearing and vacuolization on light microscopy and myelinoid

Hydroxychloroquine and proton-pump inhibitors

Proton-pump inhibitors (*e.g.* Losec®) may decrease the immunomodulating and antimalarial efficacy of hydroxychloroquine and chloroquine by interfering with the lysosomal pH of macrophages.

Namazi (2009) [157]

Retinal toxicity by hydroxychloroquine

New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of hydroxychloroquine . The risk increases further with continued use of the drug.

Marmor et al (2011) [175]

and curvilinear bodies on electron microscopy. HCQ toxicity was diagnosed and the medication was discontinued. The patient was asymptomatic within 9 months. Follow-up revealed a normal left ventricular systolic function and grade 2/4 diastolic dysfunction. Wall thickness had normalized.

Pregnancy and lactation

More than 250 pregnancies of SLE patients on HCQ resulting in live births have been reported and no increase in the rate of birth defects, retinal toxicity and ototoxicity has been demonstrated.

Data concerning lactation and HCQ treatment are rare. However, the amount of HCQ received by children through lactation seems very low. In conclusion, HCQ should probably be maintained throughout pregnancy in patients with SLE and it does not seem necessary to advise against breastfeeding.[102,103] In other diseases than SLE it is usually advised to discontinue HCQ as underlying diseases do not flare as a rule of thumb.

Hearing disorders

Alterations in hearing have been ascribed to HCQ in three patients.[120,121] It is known that chloroquines accumulate and fix selectively in melanocytes, with its ototoxicity resulting in variable injuries to the cochlear sensory hair cells, decrease in neuronal population, loss of supporting hair cells, and atrophy of stria vascularis. It is supposed that ototoxicity is associated with a similar deposit mechanism of chloroquines in the internal ear caused by a prolonged exposure time and by *high cumulative doses*.[122]

Eyes

Blurred eyesight

During the first days of treatment, the patient may experience blurred eyesight. This is perfectly innocent, has nothing to do with retina defects through overdose and can be counteracted by halving the dosage in the first week (usually 200 mg/day).[62]

Maculopathy

The most important side effect with long-term use is *maculopathy*. New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of HCQ. The risk increases further with continued use of the drug.[175] Maculopathy caused by HCQ is a double-sided disorder of the retina with defects in the field of vision. With early diagnosis and stopping the medication, the condition either recovers or progresses no further. It should be noted that the risk for maculopathy is much smaller for HCQ than for chloroquine.[108]

High or low risk of maculopathy

It is essential to base the dosage on body weight and kidney function.[105] It is recommended to go no higher than 6.5 mg/kg/day HCQ or 3.0 mg/kg /day chloroquine. Note that the body weight refers to the lean body mass (LBM). This is because chloroquines are not well absorbed in fatty tissue, so body fat should not be counted. See table 5.4.

Although HCQ can be given even if a patient already has eye defects (apart from a chloroquine maculopathy) it is usually suggested to have an eye check in the first year of treatment. This does not need to be done *before* the treatment since retina defects caused by HCQ have never been described in association with treatment of less than 9 months. The timing of the

Overdosing of HCQ is going on today .....

The importance of dosing on the basis of the lean body mass is illustrated by a study of Payne *et al*.[164] They reviewed the medical records of consecutive patients with hydroxychloroquine retinopathy in of the Emory Eye Center (Emory University, Atlanta, Georgia, USA) between 1 January 2004 and 31 December 2008. A total of seven patients were included for analysis. While every patient received 400 mg of hydroxychloroquine per day, *every patient exceeded the recommended daily dosage allowance* (6.5 mg/kg/day). The mean daily dose of hydroxychloroquine was 8.2 mg/kg/day (range: 6.8-13.6 mg/kg/day).

Payne JF et al (2010) [164]

next retina check-up depends on how high the risk of maculopathy is estimated to be. This risk is determined by the LBM, the kidney function and the length of time for which HCQ has been used.

A patient is in the *low risk group* if the dose is less than 6.5 mg/kg LBM/day HCQ and the patient has been taking the drug for less than 5 years. It is important for the upper limit of 6.5 to be lowered in proportion to any diminished kidney function.

A patient belongs to the *high risk group* if the dose is > 6.5 (or lower in the case of diminished kidney function) mg/kg LBM/day HCQ or if the patient has been taking the drug for more than 5 years.

For low risk patients, a check-up is only necessary after 5 years. For high risk patients, an annual check-up is recommended. My personal impression is that the latter recommendation is correct if the dose taken has been too high (on the basis of LBM and kidney function), but is unnecessarily stringent if the patient is only in the high risk group due to taking the drug for more than 5 years.[62]

For many patients with a weight of 60-65 kg, a dose of 400 mg HCQ per day for the first three months,

Table 5.4 *Maximum daily dose*[1] of hydroxychloroquine (HCQ) in relation to the length and lean body mass[2].
It is extremely important to decrease the dose proportionally in case of diminished kidney function (see text) and to use the real body weight in case this is less than the lean body mass (LBM).
Example: woman with lenght of 168 cm and weight of 51 kg. Weight (51 kg) is less than LBM (60 kg), so use the data on the line with a LBM of 51 kg (corresponding length of 158 cm): the maximum numbers of tablets is 11 per week and not 13 per week.

length (cm)	*lean body mass* (kg)		*maximum daily dose of HCQ* (mg)		*maximum number of 200 mg tablets/week*	
	men	*women*	*men*	*women*	*men*	*women*
150	48	43	312	280	10	9
152	50	45	319	286	11	10
154	51	47	332	306	11	10
156	53	49	345	319	12	11
158	55	51	358	332	12	11
160	57	52	371	338	12	11
162	59	54	384	351	13	12
164	61	56	397	364	13	12
166	62	58	403	377	14	13
168	64	60	416	390	14	13
170	66	61	429	397	15	13
172	68	63	442	410	15	14
174	70	65	455	423	15	14
176	71	67	462	436	16	15
178	73	69	475	449	16	15
180	75	70	488	455	17	15
182	77	72	501	468	17	16
184	79	74	514	481	17	16
186	80	76	520	494	18	17
188	82	78	533	507	18	17
190	84	80	546	520	19	18

[1] after 3-6 months, the daily dose can usually be as low as two-thirds of the maximum daily dose, or even lower, depending on the effect of hydroxychloroquine
[2] the lean body weight for men, in kilograms, is equal to 50 plus 2.3 kg for every inch over 5 feet in height; the lean body weight for women, in kilograms, is equal to 45.5 plus 2.3 kg for every inch over 5 feet in height.

followed by 200 mg/day appears to work well. If the symptoms return after reducing the dose, dosages of 200 and 400 mg can be taken on alternate days or the patient can return to 400 mg/day.

See for further details on screening for maculopathy:
Marmor MF, Kellner U, Lai TY, *et al*. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011;118:415-22. [175]

Interactions of HCQ with other drugs
HCQ can be combined with almost all drugs. Relevant interactions may occur with digoxine and proton-pump inhibitors.

Digoxin
HCQ may increase the plasma concentration of digoxine, a drug used for heart failure.

Proton-pump inhibitors
The proton pump inhibitors (PPI) omeprazole (Losec®), lansoprazole, pantoprazole, esomeprazole (Nexium®) and rabeprazole suppress gastric acid secretion by inhibiting the gastric H+/K+ ATPase at the secretory surface of the gastric parietal cells.

Chloroquine and HCQ accumulate in the acidic environment of macrophage lysosomes and raise intralysosomal pH levels, with the resultant decreased ability of macrophages to process antigens.

PPI may compete with HCQ and/or the higher lysosomal pH would inhibit the accumulation of HCQ at its site of action, thus mitigating its immunomodulatory and antimalarial effects.

The potential antagonising effect of PPI inhibitors on the efficacy of HCQ should be born in mind when facing unresponsive to antimalarials.[157]

Azathioprine
Azathioprine (Imuran®), introduced in 1963, is a purine analogue that interferes with the synthesis of DNA and RNA. Effects are a decrease of the circulating lymphocyte count and inhibition of antibody production.

Common (side) effects are leukopenia (dose dependent) and gastrointestinal symptoms such as nausea, vomiting and diarrhea. In dosages up to 150 mg a day, it is considered a rather safe drug. For many indications, it is continued during pregnancy. Potential fatal drug interactions may occur with allopurinol, a drug used for gout and hyperuricemia.

It has been widely used in the past as an immunosuppressant for organ transplantation. Today it is mainly used for autoimmune diseases such as SLE, Behçet's disease and Crohn's disease.

Price *et al* [145] performed a 6-months double blind placebo controlled trial of low dose (1 mg/kg/day) azathioprine in the treatment of 25 patients with primary Sjögren's syndrome. They found no significant change in disease activity variables when measured clinically, serologically, or histologically and conclude that low dose azathioprine does not have a role as a disease modifying agent in Sjögren's syndrome.

Case reports have been published on positive effects of azathioprine (2 mg/kg/day) combined with corticosteroids for severe central nervous system involvement, interstitial lung diseases, interstitial nephritis or autoimmune hepatitis.

Purines

The purines adenine and guanine are together with the pyrimidines thymine and cytosine the building blocks of DNA. In RNA, the complement of adenine is uracil instead of thymine. Purines are also significant components in other important biomolecules, such as ATP and NADH.

Methotrexate
Methotrexate (MTX) is a structural analogue of folic acid. Via inhibition of a folic acid reducing enzyme, MTX results in the cessation of the synthesis of various purine metabolites and also inhibits protein synthesis. High doses are used for cancer therapy while low doses are mainly used for treating rheumatoid arthritis. Low doses have little effect on T lymphocytes but mainly reduce immunglobulin levels.

Skopouli *et al* [159] performed an open, one-year pilot study of MTX (0.2 mg/kg body weight taken weekly). Seventeen patients with primary Sjögren's syndrome were enrolled. Outcome was determined on the basis of clinical and laboratory parameters. Weekly administration of MTX resulted in improvement of the main subjective symptoms (dry mouth and eyes) as well as in the frequency of parotid gland enlargement, dry cough and purpura. However, no improvement in the objective parameters of dry eyes and dry mouth were observed. Persistent asymptomatic elevation of the hepatic transaminase levels led to a dosage reduction in 7 patients (41%). The authors concluded that weekly MTX may be an acceptable form of therapy for Sjögren's patients and that double-blind trials were needed to substantiate the efficacy of this therapeutic modality. This was said in 1995 and 15 years later, such trials have not been performed to date.

Cyclosporin
Cyclosporin (Neoral®), a drug derived from a fungus, is

used for organ transplantation and many autoimmune diseases. Cyclosporin (CyA) inhibits intracellular calcineurin and as a consequence the transcription of genes for cytokines such as IL-2 in the nucleus of activated T lymphocytes.

The major adverse effect is renal toxicity which is usually dose related and reversible. Other adverse effects are hypertension, hirsutism and gingival hyperplasia. CyA has clinically important interactions with many drugs such as antifungals, calcium channel antagonists, ACE inhibitors and statins.

Grapefruit juice may dramatically increase cyclosporin concentrations. However, in the great majority of patients, CyA, in dosages not exceeding 4 mg/kg per day and the monitoring of renal function and blood pressure, is a safe and effective drug for many autoimmune diseases such as psoriasis, Behçet's disease, subacute cutaneous lupus erythematosus and inflammatory eye diseases such as various forms if uveitis.

Drosos *et al* [160] studied the efficacy and toxicity of cyclosporin A (CyA) in 20 patients with primary Sjögren's syndrome. The dose of CyA or placebo was 5 mg/kg of body weight daily. Among the 20 patients, 10 received CyA and 10 placebo. Patients treated with CyA improved in subjective xerostomia in comparison with patients treated with placebo. Subjective xerophthalmia and recurrent parotid gland enlargement *did not differ* in the two groups. No change in Schirmer's test and stimulated parotid flow rate was observed in either group. In contrast, the histopathological lesion of patients treated with CyA remained unchanged in most of the patients, while in the placebo treated group the lesion deteriorated. Laboratory parameters did not change before or after treatment in either group. The only clinical side effect observed in the CyA treated group was hypertrichosis. This study was published in 1986 and no other studies on the efficacy of CyA could be found in the literature to date.

Mycophenolate sodium and mofetil

Mycophenolate is derived from the fungus *Penicillium stoloniferum*. It inhibits inosine monophosphate dehydrogenase, the enzyme that controls the rate of synthesis of guanine monophosphate in the *de novo* pathway of purine synthesis essential in the proliferation of B and T lymphocytes.

Mycophenolates are increasingly used for the prevention of organ transplant rejection, as well as for many immune-mediated diseases.

In a open-label pilot trial, the efficacy of mycophenolate sodium (Myfortic®, MPS) was studied in patients with primary Sjögren syndrome refractory to other immunosuppressive agents. Eleven patients were treated with MPS up to 1440 mg daily for 6 months.[78] MPS treatment resulted in subjective improvement of ocular dryness and a reduced demand for artificial tears. However, no significant alterations of objective parameters for dryness of eyes and mouth were observed, although a substantial improvement of glandular functions occurred in two patients with short disease duration. In addition, treatment with MPS resulted in significant reduction of hypergammaglobulinemia and rheumatoid factors as well as an increase of complement levels and white blood cells.

In a small open study in patients with interstitial lung disease as part of various systemic auto-immune diseases, MPS was found to be safe and well tolerated. It allowed a reduction or discontinuation of prednisone (the mean daily dose decreased from 58 to 1.4 mg) without worsening of symptoms or progression of disease. The investigators concluded that MPS was less toxic and a potentially more effective agent than cyclophosphamide.[154] Further investigations about the efficacy and safety of MPS in pSS have to be performed in larger numbers of patients.

Cyclophosphamide

Cyclophosphamide (Endoxan®, Cytoxan®) is a nitrogen mustard alkylating agent. It is used to treat various types of cancer, some autoimmune disorders (*e.g.* systemic lupus erythematosus) and severe systemic vasculitis (*e.g.* Wegener's granulomatosus, polyarteritis nodosa). It is an important drug with unique beneficial effects on these diseases, but it also has major side effects, even for the relatively low doses (1-2 mg/kg body weight) that are used for autoimmune diseases and systemic vasculitis. Examples are hair loss, bone marrow suppresion, sterility, hemorrhagic cystitis, induction of lymphoma or skin cancer, and secondary infections. For these reasons, cyclophosphamide (CP) is only used for those life-threatening conditions for which it's efficacy has been firmly established.

No studies have been performed on CP for the treatment of Sjögren's syndrome in general as it is too dangerous for general application. Case reports have been published on the efficacy of CP for very severe complications of Sjögren's syndrome such as interstitial lung disease, agressive MALT lymphoma, myelopathy, cranial nerve neuropathy, and severe forms of glomerulonephritis. For some indications, CP is given intravenously once a month.

CP should only be used in Sjögren's syndrome with life-threatening complications for which no other

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare and devastating disease which results in death or an irreversible neurologic insult. Reactivation of JC virus is the cause of PML with death of oligodendrocytes resulting in demyelinating disease in the central nervous system. PML has occurred in lymphoproliferative disorders such as lymphoma, solid organ tumors, and bone marrow transplantation, and has classically occurred in profoundly immunosuppressed patients.

A surge in PML occurred in the 1980s with the onset of AIDS, highlighting the importance of T cells in the continued senescence of the JC virus in the human body. PML has also been described in patients with rheumatic diseases, including SLE, Wegener's granulomatosis, systemic sclerosis, dermatomyositis, polymyositis, and RA.

The development of PML is either due to the immuno suppressive treatment, the disease itself, or both. Recently, biologic drugs including natalizumab for multiple sclerosis and rituximab for lymphoma and SLE have been associated with the development of PML. Not all biologic drugs increase the risk of PML development. No known cases of PML associated with TNF-targeted biologic drugs have been reported.

Two patients with SLE treated with immuno-suppression and rituximab developed PML. The manufacturer estimated that 10,000 SLE patients had received rituximab therapy. Although it seems convenient to blame the biologic agents alone, it is important to recall that PML has been reported in the literature without biologic therapies in 15 cases of non-SLE rheumatic diseases on immuno-suppression and 26 cases of SLE patients on immunosuppression.

Bohren EJ et al (2008) [124]

treatment options are available.

Cytokine and cytokine-receptor-targeted therapy

TNF-targeted therapy

Infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®) inhibit the effect of TNF-α, a cytokine that plays a crucial role in causing inflammation by means of predominantly T-cell-mediated tissue damage. TNF-targeted therapies are being used for many rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, and psoriasis. The prognosis and quality of life of patients with these diseases have improved dramatically. However, safety concerns persist due to the seriousness and unexpected nature of some rare adverse events that have been seen with all 3 agents.

Infliximab

Infliximab (Remicade®) is a mouse-human chimeric antibody to TNF-α. In Sjögren's syndrome, it has been found inefficacious in a multicenter, randomized, double-blind, placebo-controlled trial with 103 patients.[79] The patients were randomly assigned to receive infliximab infusions (5 mg/kg) or placebo at weeks 0, 2, and 6 and were followed up for 22 weeks. All patients fulfilled the American-European Consensus Group criteria for primary Sjögren's syndrome and had active disease.

Etanercept

Etanercept (Enbrel®) is a human fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. In a 12-week randomized, double-blind, placebo-controlled trial with 14 patients with Sjögren's syndrome in each group, etanercept 25 mg twice weekly was clinically inefficacious.[80]

Adalimumab

Adalimumab (Humira®) is a fully human monoclonal antibody. There are no data on the efficacy of adalimumab in Sjögren's syndrome to date. As etanercept and infliximab have not been found to be efficacious, the same can be expected for adalimumab.

Lack of efficacy of TNF-targeted therapy in Sjögren's syndrome

A recent study in Sjögren's syndrome indicated that before treatment, salivary gland focus scores did not correlate with circulating TNF-α levels. Consistent with the lack of clinical benefit, enhanced markers of immune activation, frequency of cell subpopulations and aberrant cytokine profiles were not restored to normal levels by etanercept treatment. Remarkably, the levels of circulating TNF-α were significantly increased after treatment.[125]

Side effects of TNF-targeted therapy

TNF-targeted therapy in preexisting auto - immune diseases

The use of anti-TNF therapy in patients with pre-existing autoimmune diseases such as SLE, anti-TNF agents should be used with caution, especially when renal, pulmonary, or neurologic involvement is demonstrated,and should not be used in patients with preexisting interstitial pulmonary disorders.

Ramos Casals M et al (2007) [114]

Infections

Adverse events include infections *e.g.* activation of tuberculosis, pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections. In some patients, the diagnosis of histoplasmosis was initially unrecognised and antifungal treatment was delayed. Some of these patients died from histoplasmosis. There were also deaths in patients with coccidioidomycosis and blastomycosis.

The US Food and Drug Administration (FDA) has warned that for patients taking TNF blockers who present with signs and symptoms such as fever, malaise, weight loss, sweats, cough, dypsnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock, healthcare professionals should ascertain if patients live in or have traveled to areas of endemic mycoses.

Malignancies and cardiovascular disorders

An increased risk has been found for cancer, lymphoma, and cardiovascular disease.

Autoimmune diseases

There are a growing number of reports of the development of autoimmune processes related to TNF-targeted therapies, ranging from asymptomatic immunologic alterations to life-threatening systemic autoimmune diseases.[113]

A literature search by Ramos-Casals *et al* identified 233 cases of autoimmune diseases (vasculitis in 113, SLE in 92, interstitial lung diseases in 24, and other diseases in 4) secondary to TNF-targeted therapies in 226 patients.[114] The anti-TNF agents were administered for rheumatoid arthritis (RA) in 187 patients, Crohn's disease in 17, ankylosing spondylitis in 7, psoriatic arthritis in 6, juvenile RA in 5, and other diseases in 3. The anti-TNF agents administered were infliximab in 105 patients, etanercept in 96, adalimumab in 21, and other anti-TNF agents in 3.

In the patients who developed vasculitis, leukocytoclastic vasculitis was the most frequent type of vasculitis, and purpura was the most frequent cutaneous lesion. A significant finding was that one quarter of patients with vasculitis related to anti-TNF agents had extracutaneous involvement of the vasculitis.

In patients with interstitial lung disease, two specific characteristics should be highlighted: the poor prognosis in spite of cessation of anti-TNF therapy, and the possible adjuvant role of concomitant methotrexate.

In patients with preexisting autoimmune diseases such as SLE and/or vasculitis, anti-TNF agents should be used with caution, especially when renal, pulmonary, or neurologic involvement is demonstrated. Anti-TNF agents should not be used in patients with preexisting interstitial lung disorders.[114]

Clinical trial registries

WHO: http://www.who.int/ictrp/en/
NIH: http://www.clinicaltrials.gov/ct2/

Conclusion on TNF-targeted therapy

More than a million patients have been treated with the 3 currently available anti-TNF agents for a variety of rheumatic, digestive, and dermatologic diseases.
TNF-targeted therapies have been found very effica cious in controlling typical inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. Unfortunately, this is not the case for Sjögren's syndrome and SLE.

The use of anti-TNF agents has been associated with the development of autoimmune diseases such as cutaneous vasculitis, lupus-like syndrome, SLE, and

Serum sickness

Drugs that contain foreign (*e.g.* from the mouse) antibody fragments, such as infliximab and rituximab, initiate the formation of antibodies to these fragments.

This *serum sickness* reaction is the background of some of the side effects. The antibodies to these mouse fragments may also inactivate the drug. In clinical practice, the administration of these drugs is combined with some immunomodulating drug such as prednisolone or methotrexate to prevent the formation of antibodies to the drug.

interstitial lung disease. In patients with preexisting autoimmune diseases such as SLE, anti-TNF agents should be used with great caution, especially when renal, pulmonary, or neurologic involvement is demonstrated, and should not be used in patients with preexisting interstitial pulmonary disorders.[114]

IL-6 -targeted biologicals

Tocilizumab or atlizumab

Tocilizumab or atlizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) used as an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis. IL-6 is a cytokine that plays an important role in the immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer.

No data are available on therapy with this biological in Sjögren syndrome.

Anti-B lymphocyte biologicals

Rituximab

Rituximab (Mabthera®, Rituxan®) is a mouse-human chimeric antibody to the CD20 antigen. CD20 is a protein that is present on the surface of normal B-lymphocytes and almost all non-Hodgkin lymphomas. B cells are killed by the immune systems after binding of rituximab to the CD20 antigen on the cells. Rituximab has been shown to be effective in malignant diseases of B lymphocytes (B cell leukemia, B cell lymphoma) and rheumatoid arthritis. There is preliminary evidence for efficacy in many autoimmune diseases. Examples are autoimmune hemolytic anemia, pure red cell aplasia, idiopathic thrombocytopenic purpura, Evans syndrome, vasculitis, multiple sclerosis, pemphigus, pemphigoid, type 1 diabetes mellitus, SLE, and Sjögren's syndrome.

Studies in patients with Sjögren's syndrome

A small open-label study[81] and several case reports [82-91] are promising and suggest that rituximab may be effective in Sjögren's patients with non-Hodgkin lymphoma and those with severe complications that do not respond to other treatments such as severe thrombocytopenia.

Yamout *et al* described a 47-year-old female with Sjögren's syndrome and severe weakness in her legs due to *myelitis*. She had been initially treated with corticosteroids and intravenous cyclophosphamide with significant improvement but then deteriorated. The patient responded within a few days on a weekly dose of rituximab (375 mg/m^2) for four consecutive weeks and the improvement sustained at least eight months after her last dose.[89]

> ***Zumabs***
> The suffix -zumab implies that the drug is a recombinant humanized monoclonal antibody

A small double blind placebo-controlled study has shown that two infusions of rituximab 1 g (with oral and intravenous steroids to avoid serum sickness) significantly improvemed fatigue and social functioning six months later.[92]

Depletion of peripheral B lymphocytes has been found to be complete 5 weeks after onset of therapy. By 36 weeks, B cell numbers had returned, although levels were still low in some patients. Stimulated salivary flow showed a significant increase at week 12, followed by a gradual decline to just above baseline at 48 weeks. Similarly, a significant improvement of most of the visual analogue scale (VAS) scores for dry mouth and most domains of the Multidimensional Fatigue Inventory (MFI, see explanation in chapter 6) was observed, followed by a gradual decline to near baseline.[150]

Retreatment also had a significant effect on B cells, levels of IgM rheumatoid factor (RF) and stimulated salivary flow similar to the effects of the first course. VAS scores for dry mouth, MFI scores for general fatigue and SF-36 questionnaire scores for physical functioning improved significantly too.[150]

Data suggest that rituximab is effective for at least 6-9 months in patients with primary Sjögren's syndrome with active disease, improving subjective and objective symptoms. Retreatment resulted in a good clinical response.

Side effects

Mild side effects are common such as fever, chills, arthralgia, hypertension and infections. Serum sickness-like disease (purpura, arthralgia, myalgia) after rituximab infusion is not rare but may be reduced when higher doses of corticosteroids are given during treatment.[150]

Severe or fatal side effects are rare and include severe muco cutaneous reactions, progressive multifocal leuko encephalopathy (PML, see box), hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation. Nearly two thirds of cases of PML in patients with rheumatic diseases reported in the medical literature occurred in patients with SLE. Over 40% of PML cases in SLE

occurred in patients who had had minimal iatrogenic immunosuppression, suggesting that SLE itself may predispose to PML.[123] The occurrence of PML due to reactivation of JC virus infection leading to death 18 months after taking the last dose of rituximab in a patient with complicated RA, has resulted in an update of the package insert warning by the FDA.

This warning has previously noted reports of PML in patients with hematologic malignancies and autoimmune diseases for which rituximab is not approved. It has been updated to reflect the case of PML in an RA patient treated with rituximab (approved indication).

Epratuzumab

Epratuzumab is a recombinant humanised anti-CD22 monoclonal antibody. CD22 is a cell surface glycoprotein present on mature B-lymphocytes and on many types of malignant B-cells. Epratuzumab appears to function, in contrast to CD20 antibodies, more by modulation of B-cells than by their depletion capacity.

Steinfeld *et al* [148] investigated the efficacy of epratuzumab in an open-label study in patients with active primary Sjögren's syndrome. Sixteen patients received 4 infusions of 360 mg/m^2 epratuzumab once every 2 weeks, with 6 months of follow-up. 53% to 67% achieved a clinical response at 6 and 32 weeks, respectively. According to the authors, epratuzumab is a promising therapy in active Sjögren's syndrome, but further studies are needed.

Belimumab

Belimumab is a fully human IgG1 antibody directed against the B cell activating factor (BAFF) or B-lymphocyte stimulator (BLyS) protein. BLyS/BAFF is a TNF family member that upports B-lymphocyte maturation and survival. BLyS/BAFF has been implicated in the pathogenesis of autoimmune diseases and B-lymphocyte malignancies. Belimumab was developed to antagonize BLyS/BAFF activity in auto immune diseases and B-lymphocyte malignancies.126 BLyS/BAFF is made in both membrane-bound and soluble forms by myeloid cells and dendritic cells, as well as by some T cells.

Recent studies describe a higher expression of BLyS/BAFF in patients with Sjögren's syndrome.

Belimumab was well tolerated in treatment of RA over 24 weeks and SLE over 3 years. It significantly decreased rheumatoid factor (RF) levels, and modestly reduced symptoms of RA, especially in some subgroups such as patients with high disease activity, positive rheumatoid factor and no anti-TNF treatment experience. It also significantly reduced symptoms of SLE, and decreased anti-dsDNA autoantibodies during a long-period treatment.

BLyS/BAFF-blocking agents may thus also be a promising therapy for Sjögren's syndrome.[127]

According to clinical trial registries of the WHO and NIH (see box below) no clinical trials with belizumab are ongoing in patients with Sjögren's syndrome to date (accessed 22 October 2008).

Anti-T lymphocyte biologicals

Abatacept

Abatacept (Orencia®) is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7. It is licensed in the US for the treatment of rheumatoid arthritis in the case of inadequate response to anti-TNF-α therapy.

T cell activation requires two signals: binding of the T cell receptor to the antigen-MHC complex on the antigen presenting cell (APC) and a costimulatory signal provided by the binding of the T cell's CD28 protein to the B7 protein on the APC. Abatacept, which contains a high-affinity binding site for B7, works by binding to the B7 protein on APCs and preventing them from delivering the costimulatory signal to T cells, thus preventing the full activation of T cells.

Efalizumab

Efalizumab was designed to treat psoriasis. It binds to the CD11a subunit of lymphocyte function-associated antigen 1 and acts as an immunosuppressant. It is administered once weekly by subcutaneous injection. It acts to inhibit white blood cell migration out of blood vessels into tissues. Known side effects included bacterial sepsis, viral meningitis, invasive fungal disease and PML (see previous page). Four cases of PML were reported in plaque psoriasis patients, an incidence of about one in 500 treated patients. It has been withdrawn from the market.

Alefacept

Alefacept (Amevive®) is a fusion protein: it combines part of an antibody with a protein that blocks the growth of some types of T cells. Alefacept is used to control inflammation in moderate to severe psoriasis with plaque formation. It interferes with lymphocyte activation and is also being studied in the treatment of cutaneous T-cell lymphoma and T-cell non-Hodgkin lymphoma.

Alefacept inhibits the activation of CD4+ and CD8+ T cells by interfering with CD2 on the T cell membrane thereby blocking the costimulatory molecule LFA-3/CD2 interaction. It also induces apoptosis of memory-

effector T lymphocytes. Because of safety concerns, Europe has so far rejected to approve alefacept.

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*
22.12.2010	ref 167-172 on the efficacy of celecoxib in cancers and major depression.
15.12.2010	ref 166, trial on lack of effect of omega-3 and vitamine E on dry mouth
14.12.2010	Table 5.4: added that the real body weight should be used if this is less than the lean body mass.
07.10.2010	information added on chloroquine maculopathy only occurring in doses exceeding 6.5 mg/kg/day of HCQ Table added with recommended maximum dose of HCQ in relation to the length and lean body mass
05.08.2012	Refs 173 and 174 added; need incorporartion in the text Ref 175 added on new information on HCQ retinal toxicity and recommendations for early detection

Fatigue

6

Normal and abnormal fatigue

Fatigue is normal after a high level of physical exertion and forces us to take the rest that is necessary for our muscles to recover. Fatigue is the inability to maintain a specific level of normal physical activity or lack of endurance. Endurance is determined by the ability of the cardiovascular system to supply the muscles with oxygen and remove the products of metabolism.

Abnormal fatigue may be defined as a lack of endurance when we undertake a normal physical activity. However, fatigue has many more aspects and is more complex as a medical problem. It can be characterized in terms of intensity, duration, and effects upon daily function. In population-based studies, 20% of healthy adults reported persistent fatigue. Among patients with autoimmune disease, the prevalence of fatigue is in the range of 60–70%.

Weakness can be confused with fatigue, particularly since they are sometimes both present at the same time. Weakness is a reduction of normal power. If, when walking upstairs, a person is unable to go further than the first step, this is probably weakness. However, if this only occurs on the tenth step, it may be a question of fatigue.

Causes of fatigue

There are many causes of abnormal fatigue (table 6.1).

Cardiovascular disorders are a very common cause due to insufficient blood supply to the tissues.

Depression can also be a cause of fatigue. In the case of depression, a patient may already feel tired on getting up in the morning and there is no association with exertion (so no lack of endurance).

Table 6.1 Several general causes of fatigue

- heart failure
- anaemia
- depression
- metabolic disorders
- deficiency of vitamin D
- hormonal disorders
- autonomic neuropathy (low blood pressure)
- psychiatric disorders
- autoimmune disorders
- infectious diseases
- malignancies
- drugs

fatigue and Sjögren's syndrome

In Sjögren's syndrome, fatigue can have a number of different causes (see table 6.2). It is important to do everything possible to discover what the cause is, since the possibility of treating the fatigue may be directly related to this. It is unfortunately by no means always possible to discover the cause. Some causes of fatigue, such as anaemia, may in turn have a number of possible origins. Most of the disorders listed in table 6.2 speak for themselves or have already been discussed.

Distal renal tubular acidosis (DRTA) occurs in 50% of Sjögren's syndrome patients, usually in a mild form. DRTA is discussed in chapter 2. DRTA causes metabolic acidosis and compensatory hyperventilation

Table 6.2. Several causes of fatigue in Sjögren's syndrome

- inflammation of muscles and joints
- anaemia
  - · chronic inflammation
  - · iron deficiency
  - · blood loss in stomach or intestines (*e.g.* caused by medication such as NSAIDs)
  - · inflammation
  - · vitamin B12 deficiency
  - · haemolysis
- sleep disturbances
- depression
- distal renal tubular acidosis (DRTA)
  - · hyperventilation
  - · hypokalemia (muscle weakness)
- thyroid disorders
- hyperviscosity
- hypotension (low blood pressure, *e.g.* due to autonomic neuropathy)
- deficiency of vitamin D

... loss of physical functioning is independent of general fatigue, mental well-being, and depressive mood.

Hartkamp et al (2008) [6]

to correct the acidosis. More pronounced DRTA causes hypokalemia (low serum potassium). Moderate hypokalemia may cause muscular weakness, myalgia, and muscle cramps, and constipation (disturbed function of skeletal and smooth muscles, respectively). With more severe hypokalemia, flaccid paralysis, hyporeflexia, and tetany may result. Severe fatigue may be caused by the compenastory chronic hyperventliation.

Hypotension (low blood pressure) may result from autonomic neuropathy (see chapter 8) and has been found to be correlated with fatigue in Sjögren's patients.[1]

In SLE patients, vitamin D deficiency has been found to correlate with fatigue while hydroxychloroquine treatment prevented vitamin D deficiency.[2]

Fatigue without a known cause

In many patients with Sjögren's syndrome no specific cause of fatigue can be found.

Barendregt *et al* assessed fatigue in relation to depression, blood pressure, and plasma catecholamines in patients with primary Sjögren's syndrome (pSS), in comparison with healthy subjects (HS) and patients with rheumatoid arthritis (RA).[3] For the assessment of fatigue the so-called Multidimensional Fatigue Inventory (MFI) was used, a 20 item questionnaire, covering the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[10] Each dimension is represented by four items, two of which indicate fatigue and two of which are contradictory of fatigue (see box). Patients with pSS were found to be more fatigued compared with HS on all the five dimensions of the MFI. In the pSS patients, significant positive correlations between depression and the dimensions of reduced motivation and mental fatigue were found. Comparing patients with pSS with those with RA, using depression as covariate, no statistically significant differences were found between these groups.

Bax *et al* found that fatigue differed significantly from that of HS and that fatigue was equally raised in patients with primary and secondary Sjögren's syndrome.[4] Further analysis showed that 79% of the fatigue in patients with pSS could be explained by depression, total level of immunoglobulins, and thrombocyte counts ($p<0.001$). Both depression and thrombocyte counts showed a significant positive correlation, whereas levels of immunoglobulins showed a negative correlation. Increased numbers of thrombocytes is an inflammatory acute phase reaction. Despite that no significant correlation between thrombocyte counts and CRP levels were found, the finding suggests that low-grade inflammation may cause or worsen fatigue.

Godaert *et al* examined various aspects of fatigue in the daily life of female patients with pSS and SLE and in HS.[5] They compared age-adjusted, repeated measurements of fatigue across the day. General and physical fatigue was significantly higher in patients than in HS. Groups did not differ with respect to average levels of reduced motivation or mental fatigue. Both general and physical fatigue and reduced activity varied significantly during the day. Adjusting for depressive symptoms, groups showed significantly different time courses during the day. In HS and patients with SLE, fatigue first decreased and then

Multidimensional Fatigue Inventory [10]

The Multidimensional Fatigue Inventory (MFI) consists of 20 items grouped in five dimensions (facets). The responder indicates on a 1-to 5-point scale to what extent the statement applies to him or her.

general fatigue
- fit
- tired
- rested
- tire easily

physical fatigue
- do little
- take on a lot
- physically bad condition
- physically excellent condition

reduced activity
- very active
- do a lot in a day
- do very little in a day
- get little done

reduced motivation
- want to do nice things
- dread doing things
- lots of plans
- don't feel like doing anything

mental fatigue
- keep my thoughts
- concentrate well
- effort to concentrate
- thoughts easily wander

Table 6.3 PROFAD-SSI: fatigue and discomfort questionnaire (Bowman *et al* [7])

1. feeling a need to rest
2. tiredness
3. feeling exhausted
4. wanting to lie down, to sleep
5. it's hard to GET going
6. things taking an effort
7. feeling "it's a battle"
8. it's hard to KEEP going
9. feeling easily worn out
10. a lack of energy
11. a lack of strength in my muscles
12. feeling week
13. not thinking clearly
14. it's hard to concentrate
15. forgetting things
16. making mistakes
17. discomfort
18. pain
19. aching all over

The 16-item ProF consists of questions on items 1 to 16.[9]

increased, whereas a rather opposite course - at least for the first part of the day - was observed in patients with pSS. Using an ecologically valid assessment method, they demonstrated substantially higher levels of daily fatigue in SLE and pSS patients as compared to HS, thereby jeopardizing these patients' quality of life. Hartkamp *et al* studied the effect of dehydroepiandrosterone (DHEA) on fatigue, well-being, and functioning in women with pSS in a double-blind, randomised placebo-controlled clinical trial.[6] Patients from both the DHEA and placebo-treated group improved on general fatigue, mental well-being, and depressive mood but physical functioning did not change. This indicates that loss of physical functioning is independent of general fatigue, mental well-being, and depressive mood.

Bowman *et al* developed a measure of fatigue and general discomfort from words in which patients with pSS expressed their complaints of fatigue, discomfort and pain.[7] It is referred to as the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI). The questionnaire asks patients to rate the worst problems they experienced over the last two weeks with a number between 0 (not present at all) and 7 (as bad as imaginable). The 19 symptoms are listed in table 6.3.

The PROFAD-SSI was compared with other scores such as the Medical Outcome Study Short-Form 36 (SF-36®, see window and table 6.4), the brief form of the World Health Organization's Multicultural Quality of Life Instrument (WHOQOL-BRF) and the Hospital Anxiety and Depression Scale (HAD) scales.

SF-36®

The Short Form (36) Health Survey® is a survey method of patient health. The SF-36® consists of eight scaled scores, which are the sums of the questions in their section. Each scale is transformed into a 1-100 scale on the assumption that each question carries equal weight.
The eight sections are:
- vitality
- physical functioning
- bodily pain
- general health perceptions
- physical role functioning
- emotional role functioning
- social role functioning
- mental health

See table 6.4 for further details.

Fatigue, depression and fibromyalgia

The results of this study did not support the hypothesis that the fatigue associated with Sjögren's syndrome can largely be accounted for by increased levels of depression or fibromyalgia.

Bowman et al (2004) [7]

Psychosomatics, gastric ulcers and Helicobacter pylori

In general, the medical world tries to explain as much diseases, disorders and complaints as possible. As long as the explanations are based on facts it's ok. But sometimes explanations are presented for which no scientific evidence exists at all.

Very popular are explanations that are based on the way our brains work and may cause organic disease. The scientific evidence usually lacks or is very controversial. Moreover, psychosomatic explanations are often regarded as it is between your ears, it is all in your mind or even it is your own fault.

A clear example is the story of a gastric ulcer that was considered to be a psychosomatic disease in the sixtees and seventees.[8] It was ascribed to severe psychopathology.

Today we know that the bacterium Helicobacter pylori plays a crucial role in causing gastric ulcers. Moreover, eradication of this bacterium usually heals the ulcers.

The lesson to be learnt is that the medical and lay world better replaces the term "psychosomatic" by "unexplained" as long as a real psychosomatic cause of a disease has not been demonstrated.

Table 6.4 Rand Health scores for quality of life SF-36®

All of the surveys from RAND Health such as the SF-36, SF-20 and SF-12 are public documents, available without charge (for non-commercial purposes).

Instructions

Scoring the SF-36 is a two-step process. First, precoded numerical values are recoded. All items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are set at 0 and 100, respectively. In step 2, items in the same scale are averaged together to create the 8-scale scores (see the RAND website for detailed instructions). See: http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html

RAND 36-Item Health Survey 1.0 Questionnaire Items

1. **In general, would you say your health is:** Excellent 1 Very good 2 Good 3 Fair 4 Poor 5

2. **Compared to one year ago, how would your rate your health in general now?**

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing several flights of stairs	[1]	[2]	[3]
7. Climbing one flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking more than a mile	[1]	[2]	[3]
10. Walking several blocks	[1]	[2]	[3]
11. Walking one block	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. ***During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?***
(Circle One Number)

Not at all 1 Slightly 2 Moderately 3 Quite a bit 4 Extremely 5

21. ***How much bodily pain have you had during the past 4 weeks?***
(Circle One Number)

None 1 Very mild 2 Mild 3 Moderate 4 Severe 5 Very severe 6

22. ***During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?***
(Circle One Number)

Not at all 1 A little bit 2 Moderately 3 Quite a bit 4 Extremely 5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .
(Circle One Number on Each Line)

						....of the Time
	All ..	Most ..	A Good Bit ..	Some ..	A Little ..	None ..
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. ***During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?***
(Circle One Number)

All of the time 1 Most of the time 2 Some of the time 3 A little of the time 4 None of the time 5

How TRUE or FALSE is each of the following statements for you.
(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Table 6.5 The Fatigue Severity Scale Questionnaire. [12]

1. My motivation is lower when I am fatigued
2. Exercise brings on my fatigue
3. I am easily fatigued
4. Fatigue interferes with my physical functioning
5. Fatigue causes frequent problems for me
6. My fatigue prevents sustained physical functioning
7. Fatigue interferes with carrying out certain duties and responsibilities
8. Fatigue is among my three most disabling symptoms
9. Fatigue interferes with my work, family, or social life

The subject is asked to circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week (1: not appropriate; 7: agreement). The scoring is done by calculating the average response to the question.

In this study, eight facets of somatic and mental fatigue and general discomfort were compared. For somatic fatigue four facets were used: "need rest", "poor starting", "low stamina" and "weak muscles". Mental fatigue consisted of "poor concentration" and "poor memory". General discomfort was divided into "discomfort/pains" and "all-over-ache".

Patients with SLE and RA also completed the question naires. Similar patterns of responses were found between patients with pSS and SLE. The authors conclude that the PROFAD-SSI is more sensitive than the other scales to distuinguish the three rheumatic disorders from controls. The results of this study did not support the hypothesis that the fatigue associated with Sjögren's syndrome can largely be accounted for by increased levels of depression or fibromyalgia.

To further test the validity of the PROFAD-SSI, the 16-item profile of fatigue (ProF) containing the first 16 items of the PROFAD-SSI (table 6.3) was compared with the 20-item Multidimensional Fatigue Inventory (MFI).[9] In this study, it is concluded that both the ProF and the MFI distinguish between somatic and mental fatigue in Sjögren's syndrome and RA but that the ProF appeared better in resolving somatic facets of fatigue.

Segal *et al* [11] investigated the relationship of fatigue to other clinical features in pSS syndrome to identify factors contributing to the physical and mental aspects of fatigue. Fatigue was assessed with a visual analogue scale, the Fatigue Severity Scale (FSS) [12] (see table 6.5) and the ProF. Abnormal fatigue, defined as a FSS score 4, was present in 67% of the subjects. Pain, helplessness, and depression were the strongest predictors of fatigue. Depression was associated with higher levels of fatigue; however, the majority of subjects with abnormal fatigue were not depressed. Anti-SSA/Ro positive subjects were no more likely to report fatigue than seronegative subjects. The authors conclude that psychosocial variables are determinants of fatigue, but only partially account for it. Although fatigue is associated with depression, depression is not the primary cause of fatigue Sjögren's syndrome. Segal *et al* further suppose that patients who see themselves as unable to influence or control their condition are more
susceptible to fatigue and depression. However, the relationship between helplessness and fatigue remained significant after taking into account the role of depression.

Meijer *et al* [15] also showed that Sjögren's syndrome has a large impact on health-related quality of life, employment and disability as reflected by lower SF-36 scores and employment rates, and higher disability rates when compared with the general Dutch population. Furthermore, the importance of fatigue in Sjögren's syndrome was underscored by the fact that the majority of Sjögren's patients felt tired and 40% ranked fatigue as their most severe symptom. The authors conclude that fatigue should therefore be considered as an important treatment target.

From these studies it may be concluded that fatigue is one of the most severe consequences of Sjögren's syndrome with a large impact on health-related quality of life, employment and disability. Fatigue is not caused by depression.

The therapeutic approach of fatigue is discussed in chapter 5.

Fatigue

Fatigue as a cause of full or partial incapacity for work is objectified if Sjögren's syndrome has been diagnosed.

Fatigue and incapacity for work

Patients with Sjögren's syndrome are sometimes unable to (fully) work due to severe fatigue. The question then arises as to whether they are unfit for work. One of the tasks of medical examination authorities is to objectify symptoms that lead to partial or full incapacity for work, principally with the aim of preventing abuse of social benefits. In general terms, a symptom is objectified if an illness has been diagnosed of which the symptom in question is a consequence. Fatigue as a cause of full or partial incapacity for work is therefore objectified if Sjögren's syn drome has been diagnosed.

Conclusions regarding fatigue

- in Sjögren's syndrome fatigue is a very common complaint with sometimes major consequences
- it should always be endeavoured to find a cause
- even if no cause is found, this does not necessarily mean that treatment has no chance of success (see chapter 5)
- adaptation of lifestyle may improve fatigue (see chapter 5)
- fatigue can cause incapacity for work
- fatigue is associated with depression but depression is not the primary cause of fatigue Sjögren's syndrome

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. CFS is shrouded in mystery. A confusing and incorrect name used to describe this condition is myalgic encephalomyelitis (ME). Some patients with Sjögren's syndrome will have received this diagnosis in the past. As soon as the diagnosis of Sjögren's syndrome has been made, CFS is no longer valid as a diagnosis. The reason for this is that the definition of CFS requires a patient to have no diagnosed diseases that are known to cause fatigue and Sjögren's syndrome is a known cause of fatigue. In other words, CFS is a form of fatigue without a known cause.

Fatigue in CFS differs from fatigue in known diseases because it is not caused by exertion and does not improve by rest.

CFS and human gammaretrovirus

The recent discovery of a gammaretrovirus, xenotropic murine leukemia virus–related virus (XMRV), in the tumor tissue of a subset of USA prostate cancer patients has prompted Lombardi *et al* [13] to test whether XMRV might be associated with CFS in the USA. Both XMRV-positive prostate cancer and CFS, have been linked to alterations in the antiviral enzyme RNase L. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, they identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus–related virus in 67% of CFS and in 3.7% of healthy controls. Cell culture experiments revealed that patient-derived XMRV was infectious and that both cell-associated and cell-free transmission of the virus were possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. Additional tests suggested that CFS patients mounted a specific antibody response to XMRV that was absent in healthy subjects.

Erlwein *et al* [14] screened 186 CFS sufferers in the UK for XMRV provirus and for the closely related murine leukaemia virus (MLV). While the beta-globin gene was amplified in all 186 samples, neither XMRV nor MLV sequences were detected. Erlwein *et al* conclude that the discrepancy with studies from the USA may be the result of population differences between North America and Europe regarding the general prevalence of XMRV infection. This could also explain the fact that two USA groups found XMRV in prostate cancer tissue, while two European studies did not.

These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS but more studies are clearly needed.

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*
06.11.2009	information XMRV and CFS; ref 13
10.01.2010	correction of typing errors
13.01.2010	study with negative findings on XMRv and MLV added; ref 14
20.01.2010	results from ref 15
21.01.2010	detailed table with SF-36 added

Fibromyalgia

7

Fibromyalgia (FM) is a poorly-understood chronic pain syndrome characterized by widespread musculoskeletal pain, nonrestorative sleep, fatigue, psychological distress, and specific regions of localized tenderness, all in the absence of otherwise apparent organic disease.[5,12,21] FM is considered part of a huge continuum of pain and somatic syndromes.[13]

Diagnosis

The *American College of Rheumatology* established diagnostic criteria for FM in 1990.[5] Physical examination had to show that at least 11 of 18 designated tender points are painful when a specific pressure is applied (figure 7.1). These tender points may also result from distress, anxiety and depression.

Fibromyalgia patients, however, have also been found to be more tender using more sophisticated and objective measures.[13]

Prevalence

Literature data show that FM occurs more commonly in women (3.4%) than in men (0.5%).[20] The value of these data, however, is questionable. Clauw broke down the ACR criteria into the 2 elements: "chronic widespread pain" and "11 of 18 tender points".[13]

Women only met the "11 of 18 tender points" criterion more frequently than men (11x) whereas chronic widespread pain hardly occurred more frequently.

First-degree relatives of FM patients have a 8-fold increased risk of FM.[18]

Cause

It is clear that FM patients experience pain differently than the general population, and in the absence of disease.[12] The cause of FM is unknown but it is suggested that FM may result from abnormal central pain processing rather than a dysfunction in the peripheral tissues where the pain is perceived (see figure 7.2). Susceptibility for pain syndromes has been suggested to depend on about 20 genes as well as on environmental "stressors".[13] Suggested stressors are disorders with peri pheral pain (*e.g.* SLE, RA and ankylosing spondylitis), infections (with Epstein-Barr

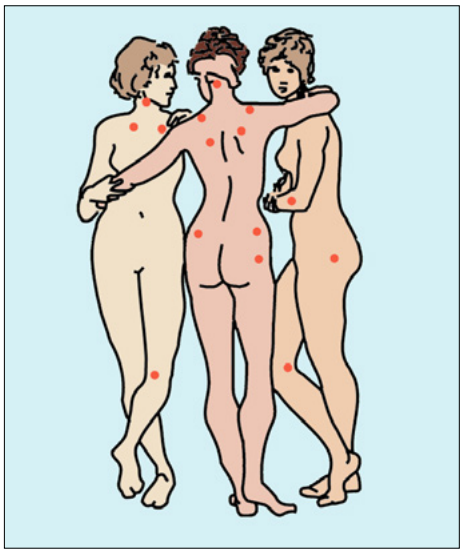

Figure 7.1 *The 18 tender points, 11 of which must be painful when pressure is applied for a diagnosis of fibromyalgia to be made.*

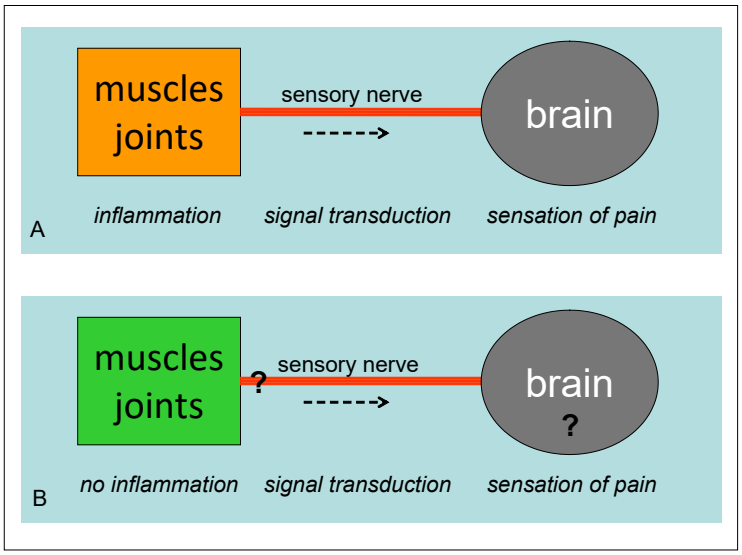

Figure 7.2 *Different causes of pain.*
A: inflammation in the muscles or joints generates sensory stimuli that travel to the brain via the nerves.
B: sensory stimuli originate in the nerves or the brain but the pain is felt in the muscles or joints.

virus or parvovirus; Lyme disease, Q fever but common cold[14]) and physical trauma.

Recent data using spectroscopic techniques suggest involvement of the central nervous system. Harris *et al* demonstrated changes in glutamate/creatine ratios within the insular cortex, an area implicated in augmented pain perception in FM, in response to treatment.[23] Wood *et al* demonstrated an abnormality in hippocampal brain metabolites in premenopausal female FM patients with no psychiatric comorbidity. A significant negative correlation between patient subjective experience of symptoms and a reduced ratio of *N-acetylaspartate* to creatine suggested a role for hippocampal pathology.[24] Emad *et al* found the same abnormality while the choline/creatine ration was normal.[25] These new data are very intruiging but it is not clear whether the abnormalities play a role in causing FM or are secondary to chronic pain.

Treatment

Important elements of treatment of fibromyalgia are aerobic exercises, a regular bed-time that guarantees adequate sleep, cognitive behavioural therapy and medication.[6-10,15-19]

Regular pain killers have little or no effect on the pain. Recent studies examining the efficacy of serotonin and norepinephrine-reuptake inhibitors (duloxetine and milnacipran) and the anticonvulsants gabapentin and pregabalin are encouraging.[11,16,17]

Abeles *et al* [21] recently systemetically reviewed treatment of FM and Uçeyler *et al* [22] treatment with antidepressants in particular. The diagnoses of FM in the reviewed papers was based on the ACR [5] or earlier criteria that do not take into account the recently described dichotomy of FM patients.[13] Abeles *et al* reviewed clinical investigations of medicinal and nonmedicinal treatments for fibromyalgia dating from 1970 to 2007.[21] They conclude that no single drug or group of drugs has proved to be particularly useful in treating fibromyalgia patients as a whole. Uçeyler *et al*, on the other hand, concluded that amitriptyline 25-50 mg/day reduced pain, fatigue, and depressiveness in patients with FM and improved sleep and quality of life. [22] They concluded that most selective serotonin as well as serotonin and norepinephrinere uptake inhibitors are probably also effective. They recommended short-term treatment of patients with FM using amitriptyline or another of the antidepressants that were effective in randomized-controlled trials. They warned that data on long-term efficacy are lacking.

Fibromyalgia and Sjögren's syndrome

A number of symptoms occurring in fibromyalgia can make it difficult to distinguish from Sjögren's syndrome. These are, with the percentage of prevalence in fibromyalgia between brackets:

- fatigue (81%)
- symptoms of dryness (36%)
- irritable bowel (30%)
- urinary urgency (25%)
- Raynaud phenomenon (17%)

In recent studies fibromyalgia was recorded in 12-55% of patients with Sjögren's syndrome.[1-4]

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Nervous system disorders

8

Disorders of the nervous system are common in patients with Sjögren's syndrome. These usually concern *sensory peripheral neuropathies* (see further) that are often mild. However, this type of neuropathy has many other possible causes and it may be difficult or even impossible to prove whether it is related to Sjögren's syndrome or not (table 8.1).

Disorders of the *central nervous system* may also occur in patients with Sjögren's syndrome (table 8.2), but it is not always certain that these are related to Sjögren's syndrome.

Relatively rare but clinically important are *paraneoplastic neurological disorders* (*e.g.* paraneoplastic subacute sensory neuronopathy, sensory ataxia, limbic encephalitis). These are believed to be remote immunologically mediated effects of a neoplastic (malignant) process, *e.g.* a small cell lung carcinoma.

Table 8.1 Some causes of peripheral neuropathy

inflammatory diseases
Guillain-Barré syndrome, SLE, Sjögren's syndrome, leprosy

metabolic and endocrine
diabetes mellitus, renal failure, porphyria, amyloidosis, liver failure, hypothyroidism

intoxication
alcoholism, drugs (vincristine, phenytoin, isoniazid, thalidomide), metals

vitamin deficiency
vitamins B1, B12, A, E

genetic disease
Friedreich's ataxia, Charcot-Marie-Tooth syndrome

paraneoplastic
mainly small-cell lung cancer, but also prostate, breast, pancreatic, neuroendocrine, bladder and ovarian cancer

various
malignancy, AIDS, radiation

Table 8.2 Neurological disorders reported in patients with Sjögren's syndrome, not implying a causal relationship

- acute transverse myelopathy [35]
- amyotrophic lateral sclerosis [37]
- aseptic meningoencephalomyelitis [33]
- brain-SPECT abnormalities [43]
- cerebellar ataxia [34]
- cerebral white matter lesions [36,44]
- chorea [31,40]
- dementia [30]
- Devic's disease (optic neuritis and longitudinally extensive transverse myelitis (LETM) [46]
- hemiparkinsonism [28]
- large tumefactive brain lesion [41]
- limbic encephalitis [47]
- multifocal leukoencephalopathy [27]
- multiple sclerosis [29]
- optic neuropathy (bilateral sequential) [26]
- Parkinsonsism [32]
- subacute inflammatory polyradiculopathy [45]

Typically, the neuropathy predates the discovery of the malignancy 3-8 months.[39] Some neurological disorders will be discussed here, without attempting to be fully comprehensive.

NERVOUS SYSTEM

The nervous system is usually anatomically divided in the *central nervous system* (CNS) consisting of the brain and spinal cord, and the *peripheral nervous system* consisting of the nerves between the CNS and the organs.

A functional division also exists: the *somatic* nervous system and the *autonomic* nervous system. The autonomic nervous system is further divided in *sympathetic* and *parasympathetic* nervous system (see also figure 8.2).

Various other disorders are also discussed such as migraine and myasthenia gravis.

A. Central nervous system disorders

The spectrum of suggested CNS involvement

includes focal (sensorial and motor deficits, brain stem, chorea, cerebellar lesions, epilepsy, migraine), non-focal (encephalomyelitis, aseptic meningitis, neuropsychiatric dysfunctions, cognitive deficits, Parkinson disease), spinal cord (myelopathy, transverse myelitis, motor neuron disease), findings or multiple sclerosis-like illness, optic neuritis and Devic's disease (table 8.1).[19,22,42,46]

Vascular disorders: vasculitis and thrombosis

Vasculitis and thrombosis (*e.g.* as part of the anti-phospholipid syndrome) are generally accepted as possible related causes of (secondary) CNS disorders in patients with Sjögren's syndrome.

Non-vascular disorders

There is no consensus on the background of CNS disorders in Sjögren's syndrome without vasculitis or thrombosis. Prevalence figures lie between 0 and 20%.[6-11,18,20] It is quite well possible, however, that CNS disorders in Sjögren's syndrome merely reflect the normal prevalence in the general population.

Generalized chorea caused by Sjögren's syndrome or an unrelated CNS vasculitis?

Min *et al* [40] described a case of a 72-yr old man who presented with generalized chorea. MRI demonstrated bilateral basal ganglia lesions. He could also be newly diagnosed with primary Sjögren's syndrome and no other diseases could be found.

Treatment was started with oral prednisolone 60 mg/day and haloperidol 1.5-2.5 mg/day. After 2 months, his symptoms completely resolved and the follow-up MRI revealed the disappearance of previous lesions.

The underlying mechanism is unknown but the mild leukocytosis at presentation and the excellent response to corticosteroid treatment suggest giant cell arteritis as the underlying vasculitis.

Despite the fact that Sjögren's syndrome was diagnosed according to the American-European criteria, the disease was only suspected and diagnosed after laboratory abnormalities suggested Sjögren's syndrome. Therefore, the relationship between the probable CNS vasculitis and the hitherto subclinical Sjögren's syndrome is uncertain. The CNS vasculitis could also be due to an unrelated vasculitis such as isolated CNS vasculitis or giant cell arteritis.

Brain-SPECT abnormalities

Le Guern *et al* [43] assessed subclinical CNS involvement in Sjögren's syndrome by comparing standard brain MRI, in-depth neuropsychological testing and ^{99m}Tc-ECD brain SPECT of patients to matched controls. Brain-SPECT abnormalities were significantly more frequent in Sjögren's patients than controls. Cognitive dysfunctions, mainly expressed as executive and visuospatial disorders, were also significantly more frequent in Sjögren's patients. A correlation was found between neuropsychological assessment and brain-SPECT abnormalities in Sjögren's patients. MRI abnormalities in patients and controls did not differ. It should be noted, however, that 8 out of 10 Sjögren's patients had hematological complications: MALT lymphoma (n=3), vasculitis (n=2), cryoglobulinemia (n=4, two of which had MALT lymphoma) and antiphospholipid syndrome (n=1). One of the remaining two patients had active peripheral neuropathy. These data suggest an organic etiology of cognitive CNS dysfunction in this subgroup of patients with Sjögren's syndrome. This is possibly not directly related to Sjögren's syndrome but due to vascular-mediated cerebral damage.

Cerebral white matter hyperintensities

Harboe *et al* [44] compared cerebral white matter hyperintensities (WMHs) in 68 unselected patients with Sjögren's syndrome and 68 age and sex matched healthy subjects (HS). Among the 68 Sjögren's patients, 50% had normal cognitive function, 24% had mild, 21% had moderate, and 6% had severe cognitive dysfunction. The Sjögren's patients with cognitive dysfunction had higher total WMH scores than those without cognitive dysfunction but this is in accordance with population-based studies of elderly people. The present study, however, showed no differences in WMH scores between Sjögren's patients and HS. It appears that cognitive dysfunction correlate with WMHs in both Sjögren's patients and HS.

White matter hyperintensities

White matter hyperintensities (WHMs) are areas of abnormal signal in the cerebral white matter detected by MRI T2-weighted sequences of fluid-attenuated inversion recovery. WHMs frequency increases with advancing age and in subjects with cerebrovascular risk factors. WHMs are typical features of multiple sclerosis but also appear more frequently in SLE and are reported in other autoimmune diseases such as the antiphospholipid syndrome and Behçets disease. Both groups showed a significant association between age and total WMH score.

> Screening for Sjögren's syndrome should be systematically performed in cases of acute or chronic myelopathy, axonal sensorimotor neuropathy, or cranial nerve involvement.
>
> *Delalande et al (2004)* [11]

Demyelinating spinal cord lesion

Yamout *et al* described a 47-year-old female with Sjögren's syndrome and severe weakness in her legs. An MRI of the brain and spine revealed a longitudinally extensive demyelinating lesion with oedema extending from Th7 to Th10. She had been initially treated with corticosteroids and intravenous cyclophosphamide with significant improvement but then deteriorated. The patient responded within a few days on a weekly dose of rituximab (375 mg/m^2) for four consecutive weeks and the improvement sustained at least eight months after her last dose.[42]

Devic's disease

Devic's disease, also known as *neuromyelitis optica* (NMO), is diagnosed on the basis of the presence of *optic neuritis*, a *myelopathy* spanning more than three vertebral segments of the cord and the presence of NMO IgG, a recently characterised *autoantibody* to the aquaporin-4 (AQ4) water-pump channel antigen.

MRI characteristics of myelitis in Devic's disease differ from myelitis seen in MS.[46] In Devic's disease spinal lesions tend to be symmetrical and span multiple vertebral segments. These lesions have been described as *longitudinally extensive transverse myelitis* (LETM). Javed *et al* [46] evaluated 16 patients with Devic's disease and 9 with LETM. They report that 4 out of these 25 patients satisfied the criteria for Sjögren's syndrome. No information is given on oral symptoms. It is remarkable that 10 of 15 patients with Devic's disease and 3 of 9 with LETM were African-Americans.

Spinal cord and optic nerves express high levels of AQ-4 (aquaporin-4). Salivary glands express high levels of AQ-5.[46] A possible explanation for the association between Devic's disease and Sjögren's syndrome, therefore, could be cross-reacting or co-occurring autoantibodies to AQ-4 and AQ-5.

Large tumefactive brain lesion

Sanahuja *et al* described a 50-year-old woman with recurrent neurologic deficits. MR imaging revealed a large brain lesion. A diagnosis of primary Sjögren's syndrome was made. The patient was treated with oral prednisone with good response. The authors suggest that large tumefactive brain lesions are a complication of primary Sjögren's syndrome.[41]

Limbic encephalitis

Limbic encephalitis, inflammation in the limbic system, is divided into two broad categories: *infectious* encephalitis and *autoimmune* encephalitis.

Limbic encephalitis is characterized by a severe impairment of short-term memory. Anterograde amnesia (a loss of the ability to memorise new events) is often associated with behavioural and psychiatric symptoms such as anxiety, depression, irritability, personality change, acute confusional state, hallucinations and complex partial and secondary generalised seizures. The symptoms typically develop over a few weeks or months, but they may evolve over a few days.[49]

Infectious limbic encephalitis

Infectious limbic encephalitis is caused by invasion of the brain by an infectious agent, usually a virus (*e.g.* herpes simplex virus).

Autoimmune limbic encephalitis

Autoimmune limbic encephalitis is caused by the immune system. There are two forms: *paraneoplastic limbic encephalitis* (PLE) and *non-paraneoplastic limbic encephalitis* (NPLE).

Paraneoplastic limbic encephalitis

Paraneoplastic limbic encephalitis (PLE) occurs in a small proportion of people with cancers, mainly cancer of the lung, thymus gland, the breast or the testis. In many cases, PLE can be diagnosed by testing for one of a group of *paraneoplastic autoantibodies* in the patient's blood.

Neurological symptoms precede the diagnosis of the malignancy in 60-75% of the patients.[49] The condition may improve or stabilise if the cancer is treated effectively, but unfortunately in many cases the tumour proves difficult to identify or the treatment does not cure the patient's neurological symptoms.[47]

Non-paraneoplastic limbic encephalitis

Non-paraneoplastic limbic encephalitis (NPLE)

> ***The limbic brain***
>
> The limbic brain includes the hippocampus, thalamus, hypothalamus and amygdala which are involved in memory and much of the behaviour related to sex, hormones, food, fight or flight responses, the perception of pleasure and competition with others. The limbic brain is the seat of higher emotions including the protection of the young and feelings such as love, sadness and jealousy.[48]

Voltage-gated potassium channel antibodies

Voltage-gated potassium channel (VGKC) antibodies cause a reduction in the number of potassium channels, decreasing the control over electrical signals operating in the brain.

Potassium channels are proteins that lie in the surrounding membrane of nerve cells in the brain and in the nerves that lead to the muscles of the skeleton, the gut and the heart. They are particularly common in the hippocampus and other limbic areas of the brain.[48]

See also *Lambert-Eaton myasthenic syndrome* at the end of this chapter.

has only been clearly recognised recently. Doctors began to identify patients who had the symptoms of paraneoplastic limbic encephalitis but who did not have any of the marker paraneoplastic antibodies in their blood and never developed a tumour. Moreover, some of these patients got better if they were treated with drugs that suppress the immune system.

Antineuronal antibodies

In many patients with auto-immune limbic encephalitis (PLE and NPLE), one or more antineuronal antibodies can be identified. Examples are anti-Hu, anti-Yo, anti-Ma2, CRMP-5 (collapsin response-mediator protein-5), amphiphysin, VGKC (voltage-gated potassium channel), VGCC (voltage-gated calcium channel), NMDAR (*N*-methyl-D-aspartate receptor) or neuropil antibodies. These antibodies show more or less associations with the kind of tumour, clinical features in addition to the limbic symptoms, and the response to treatment (see table 8.3).[49-51]

Table 8.3 Antineuronal antibodies associated with limbic encephalitis [49-51]

antibody to	*main tumours*	*additional clinical features*	*response to treatment* [a]
Hu	SCLC	sensory neuronopathy brain stem, cerebellar signs motor neuronopathy autonomic neuropathy multifocal encephalomyelitis	poor
Yo	breast, ovary	cerebellar ataxia, nystagmus	poor to moderate
Ma2	testis	hypothalamic dysfunction rostral brain stem dysfunction atypical Parkinsonism	30% improve
CRMP-5	SCLC, thymoma	cerebellar ataxia encephalomyelitis chorea, parkinsonism uveitis, retinopathy neuropathy	poor
amphiphysin	breast, SCLC	stiff person syndrome multifocal disease	poor
VGKC	nil	REM sleep behaviour disorder hyponatraemia temporal lobe epilepsy	good
VGCC	SCLC	Lambert-Eaton myasthenic syndrome	
GAD65	nil	temporal lobe epilepsy stiff person syndrome	poor
NMDAR	ovarian teratoma	psychiatric symptoms dystonia depressed consciousness hypoventilation	good
neuropil	SCLC, thymoma	multiple	good

CRMP-5 = collapsin response-mediator protein-5; NMDAR = N-methyl-D-aspartate receptor; GAD = glutamic acid decarboxylase-65; SCLC = small cell lung carcinoma; VGKC = voltage-gated potassium channel; VGCC = voltage-gated calcium channel; REM = rapid eye movement.

[a] Treatment of tumour, immunotherapy, or both.

Limbic encephalitis in Sjögren's syndrome

In *paraneoplastic* limbic encephalitis, dermatomyositis is the only autoimmune disease with an increased prevalence. Dermatomyositis is a rare disease that may also be paraneoplastic.

Very few patients (<10) with *non-paraneoplastic* limbic encephalitis and Sjögren's syndrome have been described to date.[47] This is remarkable as Sjögren's syndrome is one of the most prevalent autoimmune diseases. Therefore, the rarity of reports on patients with limbic encephalitis and Sjögren's syndrome suggests that limbic encephalitis is not part of Sjögren's syndrome but rather an example of an autoimmune disease with similar prevalences in Sjögren's syndrome and the normal population (such as Graves'disease).

Autoimmune limbic encephalitis is rare but probably under-recognised. The detection of antineuronal antibodies, therefore, may be helpful for a correct diagnosis in patients with a puzzling clinical picture.

Multiple sclerosis

In a recent study, the prevalence of multiple sclerosis (MS) in the population has been found to be 357.6/100,000 in 2004. The female:male ratio was 2.6:1 implying a prevalence of MS in women of 0.5%.[21] The prevalence of epilepsy in the population may even be as high as 1-2%.[23]

Associations between Sjögren's syndrome and multiple sclerosis are suggested in several case reports. It is clear, however, that this is not evidence of an association as both disease are common and prone to diagnostic errors.

B. Peripheral nervous system disorders

Disorders of peripheral nerves are usually divided on the basis of the number of involved nerves. In mono-neuritis one (*mononeuritis simplex*) or a few nerves (*mononeuropathy multiplex*) are involved, while in polyneuropathy many nerves are involved. The term neuropathy means disease of a nerve. Neuritis means inflammation of a nerve but this term is broadly used. Mono means single and poly means many. Peripheral refers to the part of the nervous system between the CNS on the one hand and the organs on the other. Cranial nerve neuropathies (see next column) are examples of mononeuritis simplex.

Involvement of few or single peripheral nerves

Mononeuritis multiplex

Mononeuritis multiplex is a painful asymmetric sensory and motor peripheral neuropathy (see further). The damage to the nerves involves destruction of the axon (the long part of the nerve cell) and interferes with signal conduction. Damage results from a lack of oxygen from decreased blood flow. Mononeuritis multiplex can result from many different systemic disorders such as diabetes mellitus, vasculitis of medium-size or large blood vessels, malignancies, Lyme disease, leprosy, and AIDS. It may also occur in (primary) Sjögren's syndrome but this is rare.

Cranial nerve neuropathy

Involvement of the cranial nerves is relatively rare. Cranial nerves go directly from the brain to their target areas and mainly regulate functions in the head.

In particular, there may be involvement of the 5th cranial nerve (trigeminal nerve) and the 7th cranial nerve (facial nerve). Inflammation of the 5th cranial nerve can lead to facial pain or trigeminal neuralgia. Inflammation of the 7th nerve results in Bell's palsy or facial paralysis with one-sided paralysis of facial muscles and one-sided loss of function of the salivary glands under the jaw and under the tongue (the parotid gland, however, is controlled by the 9th cranial nerve and therefore continues to function normally).

Adie's pupil is caused by damage to nerve fibres in the ciliary ganglion of the 3rd cranial nerve. The cause is thought to be inflammation (ganglionitis), for example due to a viral infection or an autoimmune disease, especially Sjögren's syndrome. It may be the first symptom of the disease to be manifested.[13-15] Adie's pupil refers to an enlarged pupil that reacts poorly to light but better to accommodation (*e.g.* focusing on one finger right in front of the nose). Adie's pupil usually occurs in one eye but may eventually affect both eyes in 20-30% of patients. The pupil is often irregular in form. Adie's pupil is mainly found in young women and the knee jerk reflexes are also often absent.

Adie's pupil should not be confused with Horner's syndrome. In Horner's syndrome there is a constricted pupil, a drooping eyelid and an inability to sweat on the affected side of the face. There is also a congenital form, where the colour of the iris differs in the two eyes, and an acquired form. In the latter form, there is a disruption of the sympathetic nerve control of the eye somewhere along its roundabout pathway which passes via the neck and upper chest cavity. This can be caused for example by an accident, sympathectomy for Raynaud phenomenon, dilatation of the aorta or one of its branches to the head, tuberculosis, a malignant tumour in the lung apex or thyroid gland surgery.

The nervous system, transmitters and receptors

The nervous system consists of a central (brain and spinal cord) and a peripheral nervous system (the nerves).

There are somatic (voluntary) and autonomic (involuntary) nerves.

The somatic nerves control the skeletal muscles and run directly from the spinal cord to the muscles and transmit signals very fast.

The autonomic nerves control the smooth muscles (*e.g.* intestines, bladder, blood vessels), the heart and the glands. They do not go directly to these organs but have a transitional station (ganglion) where the signals are communicated from one nerve to a following nerve by means of chemical substances (transmitters) by binding the transmitter to a receptor.

In the autonomic nervous system, a distinction is made between the parasympathetic and sympathetic systems.

The nervous system makes use of different transmitters and receptors (figure 3.3).

Somatic nervous system

The somatic nervous system relays the signal from the nerve to the muscles by means of the transmitter called acetylcholine that can bind to a specific acetylcholine receptor, a nicotinic type II or M-receptor.

Autonomic nervous system

In the parasympathetic nervous system, the transmission of signals also takes place by means of acetylcholine. The receptors for this in the ganglia are nictoninic type I or G-receptors while receptors on the target organ (glands, heart or smooth muscles) are muscarinic receptors. There are five types of muscarinic receptor: M1 to M5. Some organs have mainly one type (*e.g.* the salivary glands have mainly M3 receptors), while others may have several different types.

In the *sympathetic nervous system*, signals in the ganglia are also transmitted by means of acetylcholine to nictoninic type I receptors. The signal from the nerve to the target organ is likewise transmitted via noradrenaline to adrenergic receptors that differ per organ. The different adrenergic receptors are α1, α2, β1, β2 and β3. Medication prescribed to patients may be based on these. Since, for example, β1-receptors mainly occur in the heart, β1-blockers are used to slow down the heartbeat.

Entrapment neuropathy

Entrapment neuropathy refers to nerve dysfunction caused by entrapment of the nerve. A well-known example of this is carpal tunnel syndrome (see figure 8.1). The median nerve passes through a narrow tunnel in the wrist. There are many reasons why the space for the nerve may become too tight, such as an old bone fracture, arthritis or inflammation.

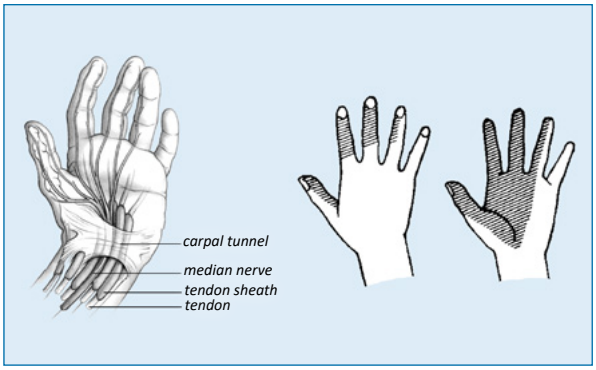

Figure 8.1 The point of entrapment of the median nerve in the wrist in carpal tunnel syndrome (left). The shaded areas indicate the localisation of symptoms (right).

The symptoms may start slowly and gradually worsen over the years and often begin at night. After sleeping for a while, the patient wakes with a hand that feels numb and swollen, with fingers that are painful and difficult to use. The symptoms are often worst in the thumb, index, middle and ring fingers.

The pain may extend upwards past the shoulders. The symptoms may start on one side but usually eventually occur on both sides. It is mainly a sensation disorder, but sometimes paralysis of the thumb and finger muscles may occur. Neurological investigation is indicated and there are various possible treatments, depending on the cause and severity.

Ultimately, surgery is often necessary to give the nerve more room. This is a relatively minor outpatient procedure. Nerve entrapment can also occur in other parts of the body, including the foot and diagonally below the knee.[5]

Involvement of multiple peripheral nerves

Peripheral polyneuropathy may results from many different disorders (see table 8.1) It occurs in about 25% of patients with Sjögren's syndrome.

Peripheral neuropathy is usually divided into sensory, motor and autonomic neuropathy, depending of the nerve fibre type that is most prominently involved but mixed types are common.

Sensory peripheral neuropathy

Sensory peripheral neuropathy is the most common form of neuropathy in Sjögren's syndrome. It is expressed in the form of a tingling, burning or numb sensation in the lower legs, feet or hands. It usually progresses no further than this and is a relatively mild disorder in many patients.[3-5]

It may be the presenting feature of Sjögren's syndrome and other features usually develop within a year. However, Stell *et al* described a 39-year old women with a 13-year history of a sensory neuropathy associated with anti-SSA/Ro antibodies, in whom there were no clinical or pathological features of Sjögren's syndrome. She also had an increased IgG and decreased C4 level.[38]

It should be realized that sensory neuropathies may also be caused by antineuronal antibodies, *e.g.* as part of limbic encephalitis (see table 8.3).

Small fibre neuropathy

Small fibre neuropathy occurs in about 3% of patients with Sjögren's syndrome.[24] It is a peripheral neuropathy characterized by the impairment of thinly myelinated Aδ and unmyelinated C-fibres. Both somatic and autonomic fibres may be involved, thus leading to sensory and autonomic neuropathies. Isolated autonomic neuropathies are rare. Symptoms of somatic nerve fibre dysfunction, such as burning, pain, and hyperaesthesia, frequently prevail over those related to autonomic nerve fibre impairment. This may explain why the term "painful neuropathy" is often used as a synonym but painful symptoms can also be a feature of large fibre neuropathies.[25]

Patients with Sjögren's syndrome-associated neuropathy often show severe neuropathic pain which is not relieved by conventional treatments.

Morozumi *et al* [28] described five patients who were treated with intravenous immunoglobulin (IVIg), 0.4 g/kg/day for 5 days. All five patients showed a remarkable improvement in neuropathic pain following IVIg therapy. Pain, assessed by the determination of mean VAS score, was reduced by 73.4% from days 2-14 following treatment. The observed clinical improvement persisted for 2 to 6 months. IVIg might be an effective treatment for pain in Sjögren's syndrome-associated neuropathy.

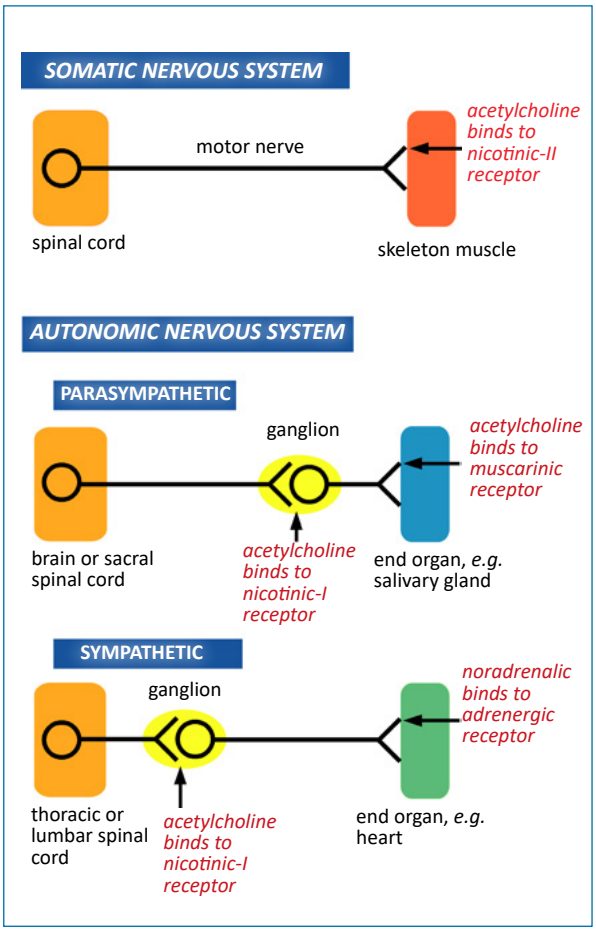

Figure 8.2 *Diagram of the nervous system with the different transmitters and receptors. Sacral spinal cord: spinal cord on a level with the sacrum, lumbar is on a level with the loins and thoracic with the chest. For further information, see text in the box above.*

Autonomic neuropathy

The autonomic nervous system (see figure 8.2 and text box) regulates many "automatic" functions of organs. Autonomic functions can be disturbed by drugs or structural changes in pre- or postganglionic neurons. Autonomic neuropathy is usually part of a generalized neuropathy.

Examples of symptoms of loss of autonomic function are postural hypotension with faintness or syncope, anhidrosis, hypothermia, bladder atony, obstipation, dry mouth and dry eys from failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males.

Hyperfunction of the autonomic nervous system may also occur. Examples of symptoms are episodic hypertension, diarrhea, hyperhidrosis, and tachycardia or brady cardia.

Motor peripheral neuropathy
Occasionally there is involvement of the motor nerves responsible for movement of muscles. This is much more serious since it can hamper movement such as walking up stairs.

C. Various Neurologic Disorders

Depression
Various studies have suggested that depression occurs more frequently than normal in Sjögren's syndrome. This is, however, by no means certain and the background to this theory is equally unclear. [5,12]

Migraine
Migraine is a unilateral (one-sided) headache often accompanied by nausea. It appears to occur more commonly than normal in people with Sjögren's syndrome.[1] There also seems to be a connection between migraine and a number of other disorders associated with Sjögren's syndrome. People with Raynaud phenomenon (bluish-white discoloration at low environment temperatures of hands and feet) and people with antiphospholipid antibodies in their blood possibly have migraine more frequently.[1] In addition to causing migraine, these antibodies may also be responsible for e.g. thrombosis in veins and arteries and low platelet levels.[2]

Myasthenia gravis and Lambert-Eaton myasthenic syndrome
Myasthenia gravis and Lambert-Eaton myasthenic syndrome are diseases characterised by weakness of the voluntary muscles caused by a defect in the transmission of nerve impulses to muscle fibres.[16,17]

Acetylcholine (ACh) is normally present in the nerve ndings in vesicles (see figure 8.3). Release of the ACh is dependent on calcium which enters the nerve endings via calcium channels. The released ACh binds to ACh receptors (AChR) on the muscle fibre. This causes the muscle fibre to contract. The ACh is quickly broken down by the enzyme cholinesterase in order to prevent the effect continuing. Nerve gases used as chemical weapons generally work by blocking the effect of the cholinesterase.

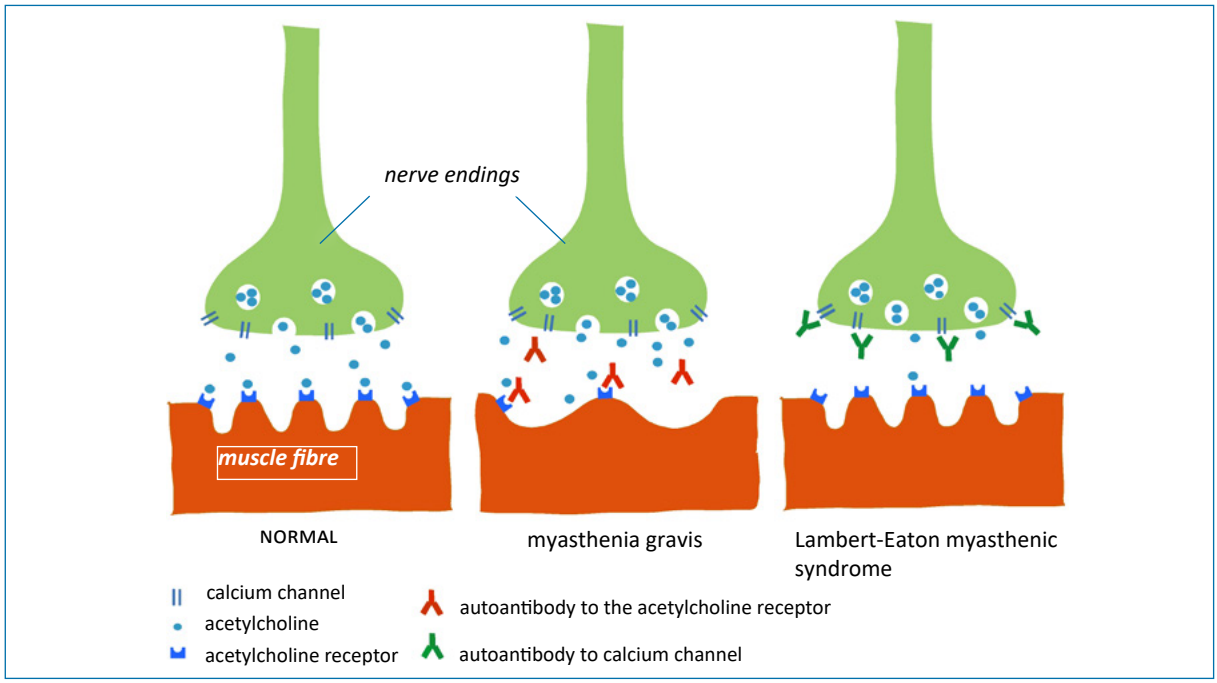

Figure 8.3 *Normal situation: acetylcholine (ACh) is released from the nerve ending and binds to the ACh receptor on the muscle fibre. This leads to contraction of the muscle fibre. The ACh is quickly broken down by the enzyme cholinesterase.*
***Myasthenia gravis**: acetylcholine is released as normal from the nerve ending but there are fewer acetylcholine receptors (AChR) present on the muscle fibre because these have been damaged by antibodies against AChR. In addition, the antibodies against the AChR can also block the receptor.*
***Lambert-Eaton myasthenic syndrome**: insufficient acetylcholine is released from the nerve ending because this is inhibited by antibodies against calcium channels.*

Myasthenia gravis

Myasthenia gravis (MG) occurs in approximately 1 in 15,000 people and affects women twice as commonly as men. In women the disease often starts between the ages of 10-30 years, in men between 40 and 60 years. Approximately 15% of MG patients also have another autoimmune disease such as rheumatoid arthritis, SLE, Sjögren's syndrome or pernicious anaemia. A usually benign tumour of the thymus gland (thymoma) is present in 10-15% of MG patients. MG can occur or be exacerbated as a side effect of certain drugs such as d-penicillamine and interferon-α. A chronic rejection (chronic *graft-versus-host)* response following a bone marrow transplant can also cause MG. In 80% of MG patients, antibodies to the acetylcholine receptor can be seen. These antibodies cause a reduction in the number of ACh receptors (AChR) and their activity. 70% of the remaining 20% of MG patients have antibodies against a tyrosine kinase receptor that is specific to muscles (MuSK, musclespecific tyrosine kinase). MuSK plays an important role in the activity of the AChR.

Typical characteristics of MG are weakness and fatigue of the skeletal (voluntary) muscles. This muscle weakness increases the longer the muscles are used. The first symptoms of MG are often double vision or drooping eyelids. The disease is treated with drugs that block the activity of the enzyme cholinesterase.

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder that occurs in 1 in 100,000 people and twice as commonly in men as in women. This disease can occur at any age but most patients are over the age of 40 years. In approximately half the patients, the disease is caused by small cell lung carcinoma. Conversely, around 3% of people with this form of lung cancer have LEMS. Other malignant diseases may also be accompanied by LEMS such as lymphosarcoma and malignant thymoma (malignant tumour of the thymus gland).

In many cases, the malignant tumour has not yet been found when the LEMS first starts and may only be discovered a couple of years later. The disease is characterised by muscular weak ness which makes it impossible to carry out normal everyday activities. The muscular weakness is often greatest in the thighs and hips. In contrast with MG, the muscular weakness improves the more the muscles are used. Many patients also have a certain degree of autonomic nervous system disorders expressed for example in the form of a dry mouth, dry eyes, reduced sweating or impotence. The possibility of LEMS should therefore be considered in men over the age of 40 years who have Sjögren's-like symptoms. This syndrome is caused by autoantibodies against the calcium channels in the nerve endings. The result is that insufficient acetylcholine is released from the nerve endings.

It can be difficult to distinguish this syndrome from myasthenia gravis. In MG the tendon reflexes are normal whereas in LEMS they are absent. There is also a difference in the effect of continuous exertion: an increase in muscular weakness in MG and a decrease in LEMS. Antibodies to calcium channels can be seen in 50-90% of patients with LEMS.

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Gastrointestinal disorders

9

The lacrimal and salivary glands, which are by definition involved in Sjögren's syndrome, are exocrine glands. Exocrine glands secrete their products to the outside of the body, in contrast with endocrine glands which deposit their secretions internally in the blood. In addition to the lacrimal and salivary glands, the exocrine glands also include glands in the stomach, intestines, airways (nose, sinuses and lungs), skin and vagina, and the pancreas and prostate. Impaired functioning of the exocrine glands can therefore have an impact on these organs too.

The gastrointestinal tract forms a relatively large part of a human being's insides (see figure 9.1). The most important function of the intestines is the absorption of food and liquid.

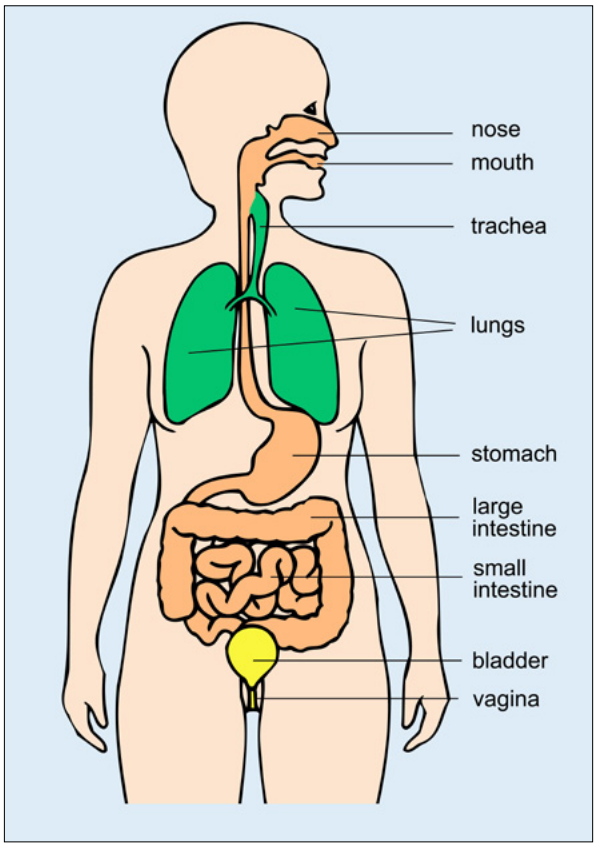

Figure 9.1 *The human body and the digestive system*

Why should people with Sjögren's syndrome have gastrointestinal problems?

If we take a look at the medical literature, there is virtually nothing to be found about the combination of Sjögren's syndrome and gastrointestinal disorders. Occasionally you find something about a form of stomach inflammation associated with vitamin B12 deficiency (*pernicious anaemia*).[1,2] The pancreas is sometimes mentioned, a gland that resembles the salivary glands in certain respects.[3-5] Since little real information is to be found about gastrointestinal disorders associated with Sjögren's syndrome, it is sometimes assumed that gastrointestinal problems do not occur with Sjögren's syndrome. Nothing could be less true.

The process of digestion starts in the mouth when you chew your food. Since the quantity and quality of saliva is often poor in Sjögren's syndrome patients, digestive problems probably begin right here.

Problems that may occur in association with Sjögren's syndrome

Difficulty in swallowing

Difficulty in swallowing food can have a variety of causes in Sjögren's syndrome. One obvious cause is dryness of the mouth and throat. In addition, the function of the oesophagus may also be impaired, not only due to dry mucous membranes but also to disorders in the pattern of contractions in the oesophagus. The cause of this may lie in the muscles themselves or in the nerve fibres that "control" the muscles.

Chronic atrophic gastritis

Chronic atrophic gastritis is the medical term for chronic inflammation of the gastric mucosa (lining of the stomach), resulting in a gradual deterioration of the structure and function of the mucosa. This can lead for example to a reduction in the production of gastric acid. This form of inflammation of the gastric mucosa also exists as a separate medical condition, but occurs more commonly in Sjögren's syndrome patients (maybe as many as 50%) than in the remainder of the

population. However, this generally concerns a mild form without detrimental consequences.[2,6,7]

Gastric ulcer

A gastric ulcer, with or without bleeding, in Sjögren's syndrome is mainly the consequence of using older types of NSAIDs. This occurs less frequently with the modern variant of NSAIDs, the selective COX-2 inhibitors (coxibs) or the combined use of NSAIDs with proton-pump inhibitors such as omeprazol. NSAIDs are discussed in chapter 5.

Functional dyspepsia

Functional dyspepsia (FD) is defined as the presence of symptoms thought to originate in the gastroduodenal region, *in the absence of organic, systemic, or metabolic disease* that is likely to explain the symptoms.[31]

Typical dyspeptic symptoms are epigastric pain, early satiety, postprandial fullness and epigastric burning. Bloating, belching, nausea, and vomiting may also occur but are less typical.

It is extremely important to realize that dyspeptic symptoms may be due to underlying peptic ulcer disease and gastroesophageal reflux disease (GERD). Malignancies of the upper gastrointestinal tract and celiac disease are less common but also important causes of dyspeptic symptoms.[30]

In patients with Sjögren's syndrome, the prevalence of FD was 65% as compared to 39% (!) in healthy controls.[28]

Impaired gastric emptying and gastroparesis

Impaired gastric emptying (IGE) and gastroparesis are defined on the basis of the time from the ingestion of a bolus of food until 50% of the bolus has been cleared from the stomach and/or the bolus is beginning to be cleared from the stomach. Gastroparesis is the more severe variant of impaired gastric emptying.[30]

IGE may be a symptom of an underlying disease such as diabetes mellitus or hypothyroidism. If no underlying cause is found, it is considered to be one of the many functional bowel disorders, in particular functional dyspepsia (see above). However, most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern.[30]

Hammar *et al* [29] found that 43% of patients with Sjögren's syndrome showed signs of IGE, while 29% fulfilled the criteria for gastroparesis. Objective signs of IGE in Sjögren's syndrome were associated with increased ESR and IgG, and the presence of rheumatoid factor. Impaired gastric emptying was, however, poorly associated with autonomic dysfunction and gastrointestinal symptoms.

Dyspepsia

Typical dyspeptic symptoms are epigastric pain, early satiety, postprandial fullness and epigastric burning.

Coeliac disease

Coeliac disease is a disease of the small bowel characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and which demonstrate improvement after withdrawal of gluten from the diet.

Forms of coeliac disease

The availability of serologic testing (see below) for coeliac disease and the common use of upper endoscopy has complicated the definition, since these tests have identified patients who appear to have the disease but have variable degrees of histopathologic changes and/or symptoms. Thus, several categories of coeliac disease have emerged. Whether these phenotypes are clinically useful remains to be determined.[32]

- the *classical form*: fully developed villous atrophy and features of intestinal malabsorption
- the *atypical form*: fully developed villous atrophy in the setting of milder clinical features such as iron deficiency, osteoporosis, short stature, and/or infertility. Despite the historical title of "atypical", this form is the most common.
- the *silent form* in which villous atrophy is found after testing asymptomatic patients (*e.g*., because of a family history of celiac disease or during an upper endoscopy performed for another reason).
- a *potential form* in those who have never had a biopsy consistent with coeliac disease, but show serologic and/or immunologic abnormalities characteristic for the disorder. This is most often detected in patients with a family history of coeliac disease.
- a *latent form* in patients who had a previous diagnosis of coeliac disease that responded to gluten withdrawal but retained normal villous architecture after gluten reintroduction. The latent form also refers to patients with elevated IgA tTG serology but normal intestinal mucosa who may subsequently develop coeliac disease.

The natural history of these various forms of coeliac disease is incompletely understood. In particular, the long-term risk of complications in patients who are asymptomatic is unclear. Such patients may also be least likely to comply with a gluten free diet.

Gluten and gliadin

Gluten in food plays an important role in causing the abnormalities seen in coeliac disease. Gluten is the protein content of wheat, barley and rye. Gliadin is the alcohol soluble fraction of gluten. Gliadin consists of large peptides that cannot be degraded by gastric and pancreatic proteases. The enzyme *tissue transglutaminase* deaminates the gliadin peptides thereby increasing the immunogenic properties.

Prevalence

Coeliac disease affects about 1% of the population, but only 10-15% of them have been diagnosed. Only people with particular HLA-antigens (HLA-DQ2 or HLA-DQ8) can acquire coeliac disease but the manifestation of the disease also depends on many other variables. Children who have had breast feeding have a lower risk, whereas the introduction of gluten in the food before the age of 4 months or after the age of 7 months increases the risk. Intestinal infections such as with rotavirus also increase the risk of developing coeliac disease.

Symptoms

Classical symptoms are diarrhoea, weight loss, or symptoms that suggest malabsorption or anaemia. Patients with atypical form of disease may present with nonspecific abdominal pain, oesophageal reflux, osteoporosis, elevated serum transaminases levels, insulin dependent diabetes mellitus, or neurological symptoms.

Diagnosis and serology

Almost all patients with atypical presentation have serum antibodies to tissue transglutaminase (tTG) but of people with antibodies to tTG, only a minority has coeliac disease.[21] Therefore, a definite diagnosis of coeliac disease requires a biopsy of the small intestine in this situation. On the other hand, a negative test for anti-tTG in a patient with *atypical* symptoms is sufficient to exclude coeliac disease.

In a patient with *classical* symptoms (see above), a small intestine biopsy is always necessary to diagnose or exclude coeliac disease as anti-tTG can be positive or negative.[21]

Diseases associated with coeliac disease [32]

Dermatitis herpetiformis is a skin disease with pruritic papulovesicles over the external surface of the extremities and on the trunk. The diagnosis is confirmed histologically by the demonstration of granular IgA deposits along the nonaffected subepidermal basement membrane. The majority of patients have anti-tTG antibodies. Dermatitis herpetiformis occurs in up to a quarter of patients with coeliac disease. Both diseases are associated with the same HLA-antigens (see before). Coeliac disease in patients with dermatitis herpetiformis is often asymptomatic, but the skin lesions in most patients respond to gluten withdrawal.

Coeliac disease is closely associated with *diabetes mellitus type 1*. About 5 percent of adults with type 1 diabetes have biopsy proven coeliac disease but many have no overt clinical manifestations. The age of onset and the severity of diabetes do not appear to be influenced by the presence of coeliac disease. Whether a gluten-free diet improves diabetes in diabetic patients with celiac disease is unclear.

Coeliac disease has been detected in up to 8 percent of patients with *selective IgA deficiency*. Selective IgA deficiency occurs in 1-2 percent of patients with coeliac disease.

The prevalence of biopsy proven coeliac disease in *Down syndrome* has been reported to be as high as 16 percent.

Coeliac disease may be associated with nonspecific mild chronic elevation in ASAT and ALAT levels. Biopsy proven coeliac disease may account for 4 percent of *abnormal liver function* tests of unexplained etiology.

There is an increased incidence of *autoimmune thyroid disease* among patients with coeliac disease. Hypothyroidism is more frequent than hyperthyroidism.

Women with untreated coeliac disease may have an increased frequency of *menstrual abnormalities* (later menarche, earlier menopause) and *infertility*. Treatment of celiac disease appears to prevent these problems.

Coeliac disease, which is often clinically unsuspected, may account for as many as 5 percent of patients with *autoimmune myocarditis* or *idiopathic dilated cardiomyopathy*. Cardiac function improved following a gluten-free diet.

Oral lesions (erythema or atrophy) and a *soreness* or *burning sensation* of the tongue have been described in association with coeliac disease and respond to a gluten-free diet.

Sjögren's syndrome and coeliac disease

A Finnish study found that coeliac disease could be diagnosed in 5 of 34 (14.7%) Sjögren's syndrome patients.[8] In a recent Canadian study, this was the case in 5 of 50 (10%) Sjögren's syndrome patients.[9]

Prognosis

Untreated coeliac disease is associated with high morbidity and increased mortality.[20]

Hypersensitivity and intolerance to food

Hypersensitivity and intolerance to food are subjects about which little is known and which is difficult to manage from both the doctor and patient's point of view.[10] Problem centre round the fact that certain foods are not tolerated. This means that consumption of the food in question can cause symptoms such as nausea, diarrhoea, pain, dizziness or skin reactions (itching, hives). Since scarcely any tests exist that prove the association between a specific food and symptoms, many patients simply exclude the suspect food from their diet and then wait and see whether the symptoms subside. If it is at matter of just one food, this method can be successful, but it is frequently a question of a large number of food items.

The exact ingredients of food products are by no means always known and the symptoms do not always occur every time the food in question is consumed. This often leads to doubt by doctors concerning the association between the food and the symptoms. It would seem that intolerance to certain foods, for whatever reason, occurs more commonly that normal in patients with Sjögren's syndrome.

Although nothing is certain, there is a possible explanation. Mucous membranes play a protective role. Since Sjögren's syndrome causes problems with mucous membranes in general, it is not unreasonable to assume that there could also be problems with the intestinal mucosa. This would result in the intestinal wall having closer contact with substances in the intestines than is normally the case. This may also play a role in the more common occurrence of hypersensitivity to medicines in Sjögren's syndrome patients.[11]

Colitis

Colitis (inflammation of the large intestine) can be the result of infection with *e.g.* salmonella or shigella) bacteria. There are also forms of colitis where the cause is unknown such as colitis ulcerosa and colitis in Crohn's disease. The term "spastic colitis" was formerly used to describe the condition which is now known as irritable bowel syndrome (see below). The name spastic colitis is misleading, however, since IBS is not an inflammatory condition of the large intestine (colon). Diverticulitis (inflammation of diverticula, pockets in the wall of the intestine) will be discussed at the end of this chapter.

Constipation

So far no publications are to be found in the medical literature in which constipation is associated with Sjögren's syndrome. When recording the symptoms of patients diagnosed with Sjögren's syndrome, it is striking that constipation symptoms often coincide with the start of other complaints. The problem is a complex one however, and it is therefore a good idea to first take a look at some of the causes of constipation.

Causes of constipation

a. too little moisture in the intestines

For normal soft bowel movements, stools should contain sufficient moisture. A diet with sufficient fibre plays an important role since fibre retains water. It may be deduced from this that constipation can occur as a result of too little dietary fibre or too little fluid in the intestines.

Table 9.1 shows how much fluid enters our gastro-intestinal tract and what happens to it. Normally around 2 litres of fluid enter the body in the form of food and drink. The salivary glands add a further 1.5 litres, the stomach 2.5 litres, bile 0.5 litre, the pancreas 1.5 litres and the intestines themselves another 1 litre. This brings the total daily fluid intake in the gastrointestinal tract to around 9 litres. Remarkably little of this disappears via faeces; most of it is reabsorbed into the body. It is the large intestine that plays the most important role in this absorption process.

Although no data are available on how much fluid enters the gastrointestinal tract of patients with Sjögren's syndrome, it may reasonably be assumed that this is considerably less than normal due to the impaired function of the intestinal exocrine glands.

On the other hand, patients with Sjögren's syndrome will usually drink far more than normal due to dryness of the mouth and this may compensate to a certain extent for the consequences of the impaired function of the exocrine glands.

b. abnormalities of intestinal muscle tissue

Muscles are classified into striated muscle (including muscles that we consciously use for movement),

Table 9.1 Amounts of fluid that enter and leave the gastrointestinal tract each day

in (ml)		*out (ml)*	
food	2000	reabsorption by intestine	8900
saliva	1500		
gastric juices	2500	faeces	100
bile	500		
pancreatic juices	1500		
intestinal juices	1000		
total	**9000**		**9000**

smooth muscles (e.g. in intestines and blood vessels which do everything automatically) and heart muscle. The smooth muscle in the intestines plays an important role in moving food along the intestinal tract. These peristaltic movements are coordinated contractions that propel the food forward. This concerted propulsion is controlled by the (autonomous or involuntary) nervous system. It is not inconceivable to suspect that these contractions are not adequately coordinated in some Sjögren's patients, giving rise to symptoms such as difficulty in swallowing, nausea, vomiting and perhaps also constipation. Inflammation of the smooth muscles possibly plays a subordinate role.

c. impaired thyroid gland function

A number of different thyroid disorders occur more frequently than normal in patients with Sjögren's syndrome, probably in one-third.[12,13] An underactive thyroid gland can be the cause of constipation and fatigue. Generally speaking, problems caused by an impaired thyroid gland are simple to treat with medication, but they first need to be diagnosed.

d. medicine

Medicine can be a significant cause of constipation and other gastrointestinal disorders. Codeine, for example, is a medication used in small quantities to treat a tickling cough. Patients with Sjögren's syn drome are particularly susceptible to a tickling cough due to dryness in the throat. Too much or too frequent use of cough mixtures containing codeine can result in constipation.

It is less well-known, however, that many drugs used to treat inflammatory conditions of *e.g.* joints (the pros ta glandin synthesis inhibitors) often cause constipation as a side-effect (sometimes days later). This is no reason for not using these drugs, but it is useful to know about this side-effect. The same type of medication can also cause inflammation of the gastric mucosa (lining of the stomach) and sometimes gastric ulcers. Inflammation of the gastric mucosa and gastric ulcers can sometimes be the cause of constipation. Drugs that contain aluminium or calcium salts can also cause constipation. Some antidepressants can cause constipation, in addition to exacerbating dryness of the mouth.

Diarrhoea

Intestinal infections are a well-known cause of diarrhoea. Food is a source of bacterial infection in the intestines. Food may already be contaminated when you buy it in the shop. Bacteria may increase to dangerous levels if food is kept too long (bacteria can also multiply in the refrigerator, albeit more slowly than at higher temperatures). Gastric acid is normally an important barrier against intestinal infection because many bacteria are unable to multiply further after spending time in the acid environment of the stomach. Some Sjögren's patients are unable to secrete gastric acid (achlorhydria), or use medication that either neutralises the acid or inhibits its production. In both situations bacteria in the food can pass through the stomach unhindered and then multiply. This means that all those who are unable to produce gastric acid or who take antacid medication run a greater risk of intestinal infections when consuming food containing excessive bacteria. To avoid problems, meat such as chicken or pork - which are often infected - should be thoroughly cooked before consumption.

Some people are unable to tolerate certain foods, without there being any clear reason why, and diarrhoea may be one of the consequences. If there is a clear link between the diarrhoea and consumption of the food, the food item in question can usually be avoided to prevent any recurrence.

Coeliac disease was discussed at the beginning of this chapter as a cause of diarrhoea.

Impaired function of the pancreas can also cause diarrhoea, particularly due to the fact that as a result of an enzyme deficiency fat is inadequately absorbed into the body and consequently has the effect of a dose of castor oil on the large intestine. This leads to diarrhoea and weight loss. Research has shown that in many Sjögren's syndrome patients the pancreas does not function 100%, but usually causes no problems.

Inflammation of the large intestine (colitis) has already been mentioned as a possible cause of diarrhoea. Blood and/or mucus often occur in the stools and this is an important signal for further investigation to exclude the possibility of bowel cancer for instance.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder in which the key symptom of abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation.[16,22] IBS was previously called spastic bowel or spastic colitis but these terms should be avoided. Functional bowel disorders are identified only by symptoms.

Subtypes of IBS are recognized by predominant stool pattern such as hard or lumpy stools, loose or watery stools, mixed and unsubtyped stools. The Rome III diagnostic criteria allow the diagnosis in patients with recurrent abdominal pain or discomfort (= uncomfortable sensation not described as pain) at

least 3 days per month in the last 3 months associated with 2 or more of the following:

- improvement with defecation;
- onset associated with a change in frequency of stool;
- onset associated with a change in form (appearance) of stool.

Supportive symptoms that are not part of the diagnostic criteria include abnormal stool frequency, abnormal stool form, defecation straining, urgency, or also a feeling of incomplete bowel movement, passing mucus, and bloating.[16] Heartburn, fibromyalgia, headache, backache, urinary symptoms, and others are often associated with IBS, but are not useful in diagnosing it.[16] The course of IBS is uncomplicated but symptoms may vary at different periods.

Constipation increases the risk of diverticulae in the sigmoid. Diverticulae may become inflamed (diverticulitis), thereby causing severe disease.

Few tests are required for patients who have typical IBS symptoms and no alarm features. Alarm symptoms such as fever, gastrointestinal bleeding,-weight loss, anaemia, abdominal mass are not due to IBS but may accompany it.[23]

The cause of IBS is unknown but it is suggested that IBS, like fibromyalgia and interstitial cystitis (bladder pain syndrome, see chapter on urogenital disorders), belongs to the central pain syndromes in which disease manifestation depends on a genetic background and environmental stressors such as peripheral pain due to inflammation or to infections.[14]

IBS occurs in 3-15% of the population. It generally starts in adulthood and is diagnosed 4x more frequently in women than in men. IBS clearly aggregates within families and first-degree relatives of IBS patients are twice as likely to have IBS as control subjects.[27] Twin studies suggest a strong environmental contribution to IBS but no significant genetic contribution.[15] In patients with Sjögren's syndrome, IBS has been found in 39-65% as compared to 9-15% in healthy controls.[28,33] Treatment consists of explanation as to why symptoms occur, adapting diet and lifestyle, or drug therapy.

Dietary fibre for IBS is poorly substantiated by clinical trials. Bran may exacerbate flatulence and not relieve pain.[24,25]

Drug therapy is directed towards the dominant symptoms. Examples are loperamide or cholestyramine (IBS with diarrhoea), psyllium or lactulose (IBS with constipation) and smooth-muscle relaxants, tricyclic antidepressants or selective serotonin reuptake inhibitors (IBS with abdominal pain).

The possible beneficial effect of probiotics is not yet

Table 9.2 Adaptation of diet and lifestyle in irritable bowel syndrome

high-fibre "bulk"-forming foods
bran, psyllium: gradually increase the quantity and drink plenty
- fibre binds moisture: liquid stools become more solid, while hard stools become softer
- in 20%: first an increase in symptoms, after several weeks an improvement

do not postpone an urge to defecate: get into the habit of going to the toilet at a regular time (after breakfast)

diet
symptoms may be exacerbated by coffee, sorbitol (sweetener), milk products, certain vegetables, cabbage

change your lifestyle: eat regularly, physical exercise, relaxation

particular symptoms
abdominal pain: if necessary smooth-muscle relaxants, tricyclic antidepressants or selective serotonin reuptake inhibitors
diarrhoea: if necessary (for preventive and occasional use): loperamide or cholestyramine
constipation: if necessary psyllium or lactulose; in general, fibre increases bloating; constipation may be treated with magnesium oxide tablets of 500 mg, 1-5x daily
flatulence
- eat slowly
- do not chew chewing-gum
- do not drink carbonated drinks or drinks containing caffeine
- do not use artificial sweeteners (sorbitol)
- do not eat cabbage

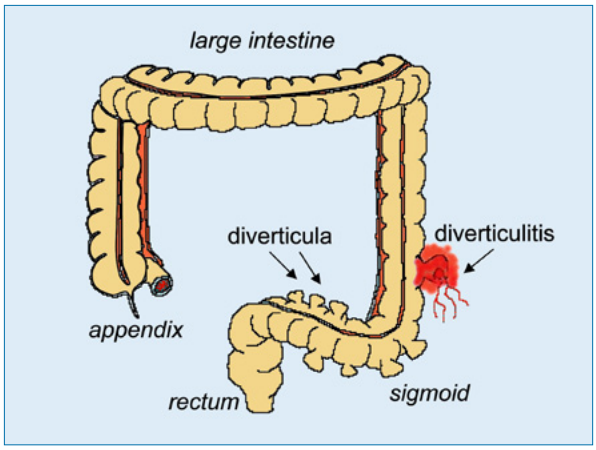

Figure 9.2 *Diverticula and diverticulitis. Diverticula particularly occur in the sigmoid, the part of the large intestine (colon) that empties into the rectum. The name sigmoid means sigma-like. Sigma is the Greek letter s:* σ

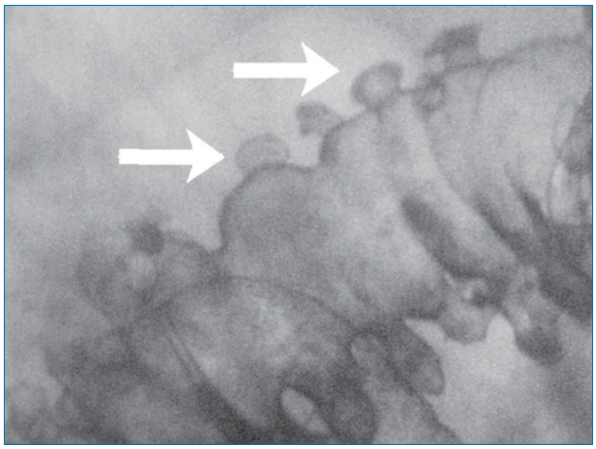

Figure 9.3 *Diverticula in the colon can be visualised on an X-ray by use of a contrast medium.*

established. Excellent guidelines for the management of IBS have recently been published by the *British Society of Gastroenterology*.[26]

Diverticulitis

Diverticula are pocket-like openings in the intestinal wall. The occurrence of diverticula is called diverticulosis (see figures 9.2 and 8.3). They most frequently occur in the sigmoid colon and especially at points where the blood vessels enter the intestine (weak points). It is estimated that 20-50% of the population over the age of 50 years in the western world have diverticula. Low-fibre diet and constipation increase the risk of diverticula.

The term diverticulitis is used when the diverticula become inflamed. This is probably caused by faecal residue in the diverticula, resulting in poor blood supply to the diverticula and allowing intestinal bacteria to set up inflammation of the diverticular wall.

The symptoms of diverticulitis depend on the severity of the inflammation. They may consist of fever, pain in the lower left abdomen and blood in the stools.[17,18]

The development of diverticula and diverticulitis has no direct link with Sjögren's syndrome. Nevertheless, the possibility cannot be excluded that diverticula may occur slightly more frequently in patients with Sjögren's syndrome than normal, perhaps because Sjögren's patients suffer more commonly from constipation, due on the one hand to the disease itself and on the other to the use of anti-inflammatory drugs (the prostaglandin synthesis inhibitors).

Treatment of diverticulitis in Sjögren's syndrome is the same as in people without Sjögren's syndrome. In addition, a high-fibre diet is important to prevent constipation.[19]

Muscarinic M3-receptors (see chapter 3) play a role in the contraction of the muscles in the intestinal tract and urinary bladder. It is therefore possible that antibodies to M3-receptors, that are now known to cause dryness of the eyes and mouth in Sjögren's syndrome, may also affect the functioning of the intestines and bladder.

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Latest additions or modifications (date: dd.mm.yyyy)

date	***addition/modification***
21.09.2010	data on functional dyspepsia, impaired gastric emptying and gastroparesis; references 28-31
22.09.2010	information on coeliac disease extended
03.10.2010	information on irritable bowel syndrome updated

Liver and pancreatic disorders

10

LIVER DISEASES

Liver diseases have been found in about a quarter of patients with Sjögren's syndrome.2,3,9,10 These are both chronic infections with hepatitis C virus (HCV) in regions with a high prevalence of HCV infection, such as the Mediterranean area (13%), and autoimmune liver diseases (table 10.1). Primary biliary cirrhosis (PBC) is the most frequent (4-10%) autoimmune liver disease in Sjögren's patients. Less frequent are autoimmune hepatitis (2-4%) and primary sclerosing cholangitis.

Table 10.1 Diseases of the liver and pancreas that occur more often in patients with Sjögren's syndrome than in the general population

- autoimmune hepatitis type 1
- granulomatous hepatitis
- hepatitis C
- primary biliary cirrhosis
- autoimmune cholangitis
- primary sclerosing cholangitis
- autoimmune pancreatitis

A. Autoimmune liver diseases

Autoimmune liver diseases include a spectrum of diseases which comprises both cholestatic and hepatitic forms:

1. autoimmune hepatitis
2. primary biliary cirrhosis and autoimmune cholangitis
3. primary sclerosing cholangitis
4. overlap syndromes

In the overlap syndromes, hepatitic and cholestatic damage coexist. The autoimmune liver diseases are characterized by an extremely high heterogeneity of presentation, varying from asymptomatic, acute (as in a subset of autoimmune hepatitis) or chronic (with aspecific symptoms such as fatigue and myalgia in autoimmune hepatitis or fatigue and pruritus in primary biliary cirrhosis and primary sclerosing cholangitis).[1]

1. Autoimmune hepatitis

Two types (1 and 2) of autoimmune hepatitis are distinguished (table 10.2). Antinuclear antibodies (ANA) and anti-smooth muscle antibodies (SMA) mark type 1 AIH, while liver kidney microsomal antibody type 1 (LKM1) and liver cytosol type 1 (LC1) are the serological markers of type 2 AIH.

Clinical manifestations

Patients may present with nonspecific symptoms of varying severity, such as fatigue, lethargy, malaise, anorexia, nausea, abdominal pain, and itching. Arthralgia involving small joints is common. Physical examination may reveal no abnormalities, but it may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease.

Rarely, AIH presents as fulminant hepatic failure. Patients with occult disease may have undetected cirrhosis and present only when decompensation occurs.

Many patients with an acute presentation have histological evidence of chronic disease in the liver biopsy, indicating that they have had antecedent subclinical disease.[4,5]

Histopathology

AIH is characterized by a lymphocytic infiltrate. There may be an abundance of plasma cells and eosinophils are frequently present. The portal lesion generally spares the biliary tree.

Fibrosis is present in all but the mildest forms of autoimmune hepatitis. In advanced disease, the fibrosis is extensive, and with the distortion of the hepatic lobule and the appearance of regenerative nodules, it results in cirrhosis.[4,5]

Diagnosis

The detection and characterization of non-organ specific autoantibodies plays a major role in the diagnostic approach of autoimmune liver disease. In the presence of a compatible histologic picture, the diagnosis of AIH is based on characteristic clinical and

Table 10.2 Characteristics of autoimmune hepatitis types 1 and 2 (Krawitt 4)

variable	*type 1*	*type 2*
characteristic autoantibodies	ANA smooth-muscle antibody anti-actin antibody autoantibodies to soluble liver antigen and liver–pancreas antigen atypical p-ANCA	antibody to liver–kidney microsome 1 antibody to liver cytosol
geographic variation	worldwide	worldwide; rare in North America
age at presentation	any age	predominantly children and young adults
sex of patients	female in about 75% of cases	female in about 95% of cases
association with other autoimmune diseases	common	common
clinical severity	broad range	generally severe
histopathologic features at presentation	broad range	generally advanced
treatment failure	infrequent	frequent
relapse after drug withdrawal	variable	common
need for long-term maintenance	variable	about 100%

biochemical findings, circulating autoantibodies and abnormalities of serum globulins.[4,5]

High-titre smooth-muscle antibodies have been found indicators for future development of AIH.[8]

Disease associations

AIH may occur in conjunction with a variety of autoimmune disorders.[6] Examples are ulcerative colitis, celiac disease, rheumatoid arthritis, vitiligo, discoid lupus erythematosus, systemic sclerosis, autoimmune hemolytic anemia and Sjögren's syndrome. Arthralgia of small joints is common, and arthritis may be particularly trouble some.

One presentation of AIH is in the setting of medications, or herbal agents, used for other diseases. Minocycline and statins may trigger AIH.[4,5]

Treatment

Treatment options rely on immunosuppressive therapy. Standard medications for initial and maintenance regimens are still considered to be prednisolone alone or in combination with azathioprine. in autoimmune hepatitis (AIH) and on ursodeoxycholic acid in cholestatic conditions. The worst outcome is end stage of liver disease for which liver transplantation remains the only therapeutical approach.[4,5]

Prognosis

Long periods of subclinical disease may also ensue after presentation. In patients who have a spontaneous or pharmacologically induced remission, the histologic findings may revert to normal or inflammation may be confined to portal areas. In this setting, cirrhosis may become inactive and fibrosis may diminish or dis appear.

Complications of AIH are those seen in any progressive liver disease and primary hepatocellular carcinoma is an expected, although uncommon, consequence. There are no established guidelines for hepatocellular carcinoma screening in cirrhosis associated with AIH. A reasonable approach would be surveillance with an ultrasound and -fetoprotein every year.[4,5]

2. Primary biliary cirrhosis and autoimmune cholangitis

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease in progressive bile-duct injury from portal and periportal inflammation can result in progressive fibrosis and eventual cirrhosis. Evidence to date suggests that immunological and genetic factors might cause the disease. Affected individuals are typically middle-aged women with asymptomatic rises of serum hepatic biochemical variables. Fatigue, pruritus, or unexplained hyperlipidaemia at initial presentation suggests PBC. Antimitochondrial antibodies (AMA) are nearly diagnostic of the disease. Disease identification

Table 10.3 Extrahepatic autoimmune disorders associated with primary biliary cirrhosis [11]

disorder	*prevalence (%)*
keratoconjunctivitis sicca	75
renal tubular acidosis	50
gallstones	30
arthritis	20
thyroid disease	15
systemic sclerosis	15
Raynaud's phenomenon	10
CREST syndrome	5

is important because effective medical treatment with ursodeoxycholic acid can halt disease progression and extend survival free of liver transplantation.[11]

Clinical manifestations

.....

Histopathology

Histological classification schemes have categorised the disease into four stages.

Stage 1 is associated with portal-tract inflammation frompredominantly lymphoplasmacytic infiltrates, resulting in destruction of septal and interlobular bile ducts up to 100 µ in diameter. Focal-duct obliteration with granuloma formation has been termed the florid duct lesion, and is judged almost pathognomonic for primary biliary cirrhosis when present.

Stage 2 entails periportal extension of inflammation. Cholangitis, granulomas, and ductular proliferation are most typically seen.

Stage 3 is dominated by septal or bridging fibrosis. Ductopenia (defined as loss of >50% of interlobular bile ducts) becomes more frequent, resulting in cholestasis and raised hepatic copper deposition within periportal and paraseptal hepatocytes.

Stage 4 accords with biliary cirrhosis. Because of increased sampling variability from liver biopsy specimens in the disease, the highest recognised stage should be used to establish extent of involvement.[11]

A diagnosis of antimitochondrial antibody-negative primary biliary cirrhosis cannot be made without a liver biopsy specimen.[11]

Diagnosis

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Disease associations

.....

Treatment

.....

Prognosis

.....

Autoantibodies in PBC

Between 90% and 95% of people with antimitochondrial antibody in serum, at titres of 40 or greater, have PBC. Seropositivity for this antibody is not specific to the disease, but remains highly sensitive (98%). ANA and smooth muscle antibody arise in 35% and 66% of patients with PBC, respectively.

Serum anticentromere antibodies in patients affected by the CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasias) are noted in 10–15% of instances. Absence of seropositivity for antimitochondrial antibody in patients with clinical features suggestive of PBC has been termed autoimmune cholangitis. Serum autoantibodies, including antinuclear antibody, smooth muscle antibody, and anticarbonic anhydrase, are usually present. Of note, no differenceseems to be present in natural history or responsiveness to ursodeoxycholic acid treatment in patients with autoimmune cholangitis compared with those with antimitochondrial antibody-positive PBC. An overlap syndrome between PBC and autoimmune hepatitis arises in fewer than 10% of patients.

It has been found that patients with IF-AMA usually develop symptomatic PBC upon a 5 year follow-up. It is likely that patients without IF-AMA, who express PBC-specific AMA, are in early, asymptomatic stage of the disease. High-titre IF-AMA is the most specific indicators for PBC.[8]

PBC is a rather uncommon development in patients with primary SS. The disease appears to be pathologically mild, with a propensity for slow progression, as assessed clinically, biochemically, and histologically.[10]

Standard medication is ursodeoxycholic acid and liver transplantation in end stage liver disease.[4,5]

[antimitochondrial antibodies (AMA) are associated with PBC / increased serum IgM]

3. Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic progressive cholestatic liver disease characterized by inflammation and fibrosis of bile ducts, leading to the formation of bile duct strictures. PSC eventually develops into cirrhosis, portal hypertension and hepatic failure in the majority of patients.[20]

Secondary sclerosing cholangitis is characterized by a similar biliary stricturing process due to identifiable causes such as long-term biliary obstruction, infection, and inflammation which in turn leads to destruction of bile ducts and secondary biliary cirrhosis. IgG4-positive sclerosing cholangitis might represent a separate entity.

Clinical and diagnosis presentation of PSC

The clinical presentation of PSC is variable. Symptoms include right upper quadrant abdominal discomfort, fatigue, pruritus, and weight loss. Episodes of cholangitis (*i.e.*, fever and chills) are uncommon features at presentation, in the absence of prior biliary surgery or instrumentation such as endoscopic retrograde cholangiography (ERC).

Physical examination is abnormal in about half of symptomatic patients at the time of diagnosis; jaundice, hepatomegaly, and splenomegaly are the most frequent abnormal findings. Many patients with PSC are asymptomatic with no physical abnormalities at presentation. The diagnosis is made incidentally when persistently cholestatic liver function tests are investigated. 60-80% of patients with PSC have concomitant inflammatory bowel disease, most often ulcerative colitis.

Magnetic resonance cholangiography (MRC), which is non-invasive and avoids radiation exposure, has become the diagnostic imaging modality of choice when PSC is suspected. Sensitivity and specificity of MRC is ≥80% and ≥87%, respectively, for the diagnosis of PSC. However, patients with early changes of PSC may be missed by MRC, and ERC still has a useful role in excluding large duct PSC where MRC views may not be optimal.[20]

No specific marker is found in PSC, since anticytoplasmic neutrophil antibodies with perinuclear pattern (atypical p-ANCA) are also detected in a substantial proportion of type 1 AIH cases.

Course of PSC

When cirrhosis is present in a patient with PSC, *portal hypertension* will gradually develop.

Hepatic osteodystrophy is a metabolic bone disorders associated with chronic liver diseases. The diagnosis is made by bone mineral density measurement whereby osteopenia is characterized by a T-score between 1 and 2.5 standard deviations below the density observed in young normal individuals, and osteoporosis as a T-score beneath 2.5. The incidence of *osteoporosis* in PSC is between 4 and 10%.

Patients with PSC are at risk for developing *cholangiocarcinoma*. The 10-year cumulative incidence is 7-9% in recent studies.

The estimated 10-year *survival* for PSC patients is about 65% in a population based study, but large individual variations exist.

Treatment of PSC

Treatments which are efficacious in other cholestatic liver diseases have been tested in PSC with a limited degree of success.

Ursodeoxycholic acid (UDCA) is an effective treatment of primary biliary cirrhosis. UDCA has, therefore, also been investigated for the treatment of PSC. Small pilot trials of UDCA demonstrated biochemical and histological improvement in PSC patients using doses of 10–15 mg/kg/day. However, the role for UDCA in slowing the progression of PSC-related liver disease is as yet unclear and high dose UDCA may be harmful (see Chapman *et al* [20]).

Treatment with corticosteroids and other immunosuppressant agents have not demonstrated any improvement in disease activity or in the outcome of PSC. Small randomized, placebo-controlled or pilot trials have investigated the role of agents with immunosuppressive potency like prednisolone, budesonide, azathioprine, cyclosporin, methotrexate, mycophenolate, and tacrolimus, agents with TNFα antagonizing effects like pentoxifyllin, etanercept and anti-TNF monocolonal antibodies and antifibrotic agents like colchicine, penicillamine, or pirfenidone. There is no evidence that any of these drugs are efficacious and, therefore, none can be recommended for classic PSC.

Liver transplantation for PSC is highly successful with 5-year survival rates of about 85% in patients receiving deceased donor allografts. Disease recurrence occurred in 20-25%, after 5-10 years in patients, from the transplant procedure.[20]

4. Overlap syndromes

Clinical, histologic, and serologic profiles of overlap syndromes differ from the classic features of AIH, PBD, and PSC. Many different terms have been used to describe patients with features of both AIH and PBC.[5]

B. Other liver diseases

1. Granulomatous hepatitis

A possible association between granulomatous hepatitis and Sjögren's syndrome has been suggested.7 Granulomatous hepatitis is a histological description and may have many causes such as sarcoidosis and hypersensitivity reactions to drugs.

2. Hepatitis C

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PANCREATIC DISEASES

1. Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a rare disorder often associated with multiple autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease and Sjögren's syndrome. The cause and patho genesis are not known. Antinuclear antibodies (ANA) or elevated serum levels of IgG4, a systemic autoimmune disease association and positive response to oral steroid therapy support the idea of autoimmune mechanisms involved in the pathogenesis of AIP.[12]

Clinical presentation

AIP is a disease with usually mild symptoms, severe attacks of abdominal pain are not typical. Typically, pancreatic calcifications and pseudocysts are absent.

Jaundice and/or pancreatic mass are frequent signs, and both make the differential diagnosis with pancreatic cancer difficult.19 AIP is rarely associated with diabetes mellitus and exocrine pancreatic dys - function.

Presentation as a pancreatic mass

Single or multiple pancreatic masses have been described in patients with Sjögren's syndrome mimicking pancreatic carcinoma. The mass may compress the main pancreatic duct, or common bili duct causing jaundice. Infiltrates are similar to those in the salivary glands consisting of CD4-positive T-lymphocytes. Failure to recognize the real nature of the pancreatic mass (pseudotumor) can lead to inappropriate surgery.

Histology

Periductal lymphoplasmacytic infiltration is invaribly present in AIP, followed in order of frequency by periductal fibrosis and venulitis. These changes are absent in chronic pancreatitis associated with pseudo cysts, calculi, pancreas divisum and/or duodenal wall inflammation.[18]

Diagnosis

The lack of specific biochemical markers is a major drawback in the diagnosis of AIP. The Japan Pancreas Society proposed diagnostic criteria for AIP as the presence of antibodies, pancreas enlargement and pancreatic duct narrowing, lymphoplasmatic infiltration, response to corticosteroid therapy, and association with other autoimmune diseases such as autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, sialoadenitis, inflammatory bowel disease and Sjögren syndrome.[19]

Serology

Autoantibodies to carbonic anhydrase (CA), an enzyme abundantly present in the epithelium of pancreatic ducts, may be a useful tool for the differential diagnosis of pancreatic cancer and other pancreatic disorders. Compared with the prevalence of antibodies to carbonic anhydrase II (anti-CAII) in healthy subjects, a significantly higher prevalence of the antibody was detected in patients with autoimmune pancreatitis (88.9%), Sjögren's syndrome (67.6%), and alcoholic chronic pancreatitis (45.8%). No positiveresults were obtained among patients with pancreatic cancer.[15]

Association with cholangitis

AIP is frequently associated with sclerosing cholangitis (SC). SC with AIP has a cholangiographic appearance that is often confused with primary SC (PSC) but only SC responds well to corticosteroid therapy. Detailed study of cholangiographic findings allows discrimination of SC with AIP from PSC.[16]

Treatment and prognosis

Oral prednisolone is effective in most cases to reduce the size of the mass and the clinical problems.[13,14] AIP treated with oral prednisolone has a favorable long-term outcome based on the morphological findings and assessments of pancreatic function.[17]

A case has been reported of a patient with primary Sjögren's syndrome who developed relapsing AIP to steroids but responded successfully to rituximab therapy.[12]

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Pulmonary disorders

11

Introduction

The course of Sjögren's syndrome may be complicated by various lung disorders. In this context, primary Sjögren's syndrome (pSS) must be distinguished from secondary Sjögren's syndrome (sSS) as patients with sSS by definition have a second systemic auto immune disease. These are usually systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis, diseases in which lung involvement is common.

The lungs are composed of several tissues (figure 11.1). The alveoli (air sacs), connective tissue, bronchi and smal ler airways, blood vessels, nerves and pleura. Each of these tissues can become inflamed. In addition, the lungs may become infiltrated with cells or substances that do not belong there.

In interstitial lung disease (ILD), the tissue between the alveoli becomes inflamed hampering the gas exchange between the alveolar air and the blood.

Several ILDs have been shown to occur more common in patients with Sjögren's syndrome than in the general population. Lung biopsy is often required to establish a pulmonary diagnosis. Shi *et al* compared the results of transbronchial lung biopsies (TBLB) with surgical lung biopsies.[23] None of 7 TBLB cases showed changes considered to be the correct diagnosis based on the surgical biopsy. Small airway involvement was found in none of the TBLB specimens of the 6 patients who had definitive small airway involvement established via surgical lung biopsy.[23]

Table 11.1 Interstitial lung diseases in 18 patients with primary Sjögren's syndrome and pulmonary disease [3]

diagnosis	*patients (n,%)*
nonspecific interstitial pneumonia	5 (28)
organizing pneumonia	4 (22)
usual interstitial pneumonia	3 (17)
lymphocytic interstitial pneumonia	3 (17)
primary pulmonary lymphoma	2 (11)
diffuse interstitial amyloidosis	1 (6)

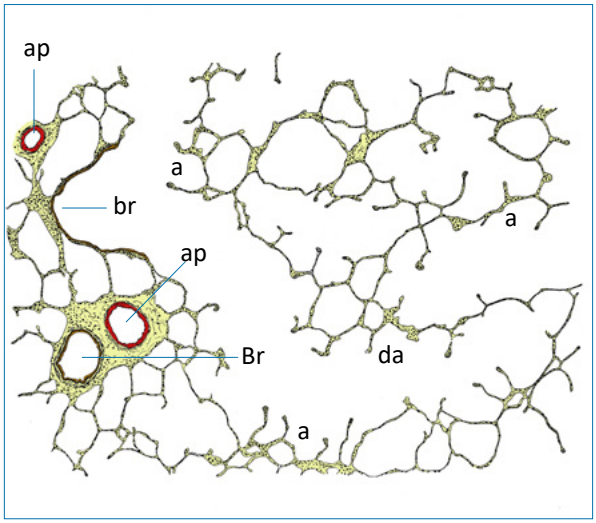

Figure 11.1 Section of normal lung tissue showing alveoli (a), small alveolar duct (da), bronchiolus (br), bronchus (Br) and branches of the pulmonary artery (ap).

Overall involvement of the respiratory tract is more common in sSS but ILD is more common in pSS.[13]

In Sjögren's syndrome, general dryness and lack of airways secretion cause the major problems of hoarseness, cough, and bronchitis.

Ramos-Casals *et al* found lung involvement in 112 out of 1010 (11%) patients.4 In his study, lung involvement was defined as persistent cough and/or dyspnea, with chronic diffuse interstitial infiltrates on x-ray, altered pattern on pulmonary function studies, and/or evidence of pulmonary alveolitis/fibrosis in computed tomography scans. No further details on the pulmonary diagnosis were given.

Transbronchial versus surgical lung biopsy

Transbronchial lung biopsies (TBLB) tend to contain more nonspecific findings and none of 7 TBLB cases showed changes considered to be the correct diagnosis based on the surgical lung biopsy.

Shi et al. 2009 [23]

Interstitial lung diseases

Interstitial lung diseases (ILDs) are nonmalignant disorders and not caused by identified infectious agents. In ILD, the tissue between the alveoli becomes inflamed making it difficult to breathe. ILD includes more than 200 individual diseases.

Many approaches to classification exist. For each ILD there may be an acute phase, and there is usually a chronic one as well. The chronic stage is called by a variety of names, including interstitial pulmonary fibrosis, pulmonary alveolar fibrosis, and idiopathic pulmonary fibrosis.

The *American Thoracic Society* and the *European Respiratory Society* have outlined a joint classification system and terminology that will be used in this chapter.[11,12]

Causes

ILDs are associated with occupational and environmental exposures, radiation, drugs and autoimmune diseases or have no known cause ("idiopathic"). Several idiopathic pneumonias are recognized. These are:

- nonspecific interstitial pneumonia (NSIP)
- usual interstitial pneumonia (UIP) / idiopathic pulmonary fibrosis (IPF)
- idiopathic pulmonary fibrosis (IPF) / cryptogenic fibrosing alveolitis (CFA)
- desquamative interstitial pneumonia (DIP)
- respiratory bronchiolitis associated interstitial lung disease (RB-ILD)
- acute interstitial pneumonia (AIP)
- lymphocytic interstitial pneumonia (LIP)
- cryptogenic organizing pneumonia (COP) / organizing pneumonia (old name: BOOP)

In general, UIP is the most prevalent of the idiopathic interstitial lung diseases. Less common types of idiopathic interstitial lung diseases include NSIP and LIP.

Among the ILDs of known cause, the largest group comprises occupational and environmental exposures. Examples are silica dust, chemical fumes and chlorine gases or organic substances such as grain dust, dust frombird and animal droppings. Radiation therapy for lung orbreast cancer may cause lung damage after many years. Some drugs can damage the interstitium of the lungs such as methotrexate and nitrofurantoin.

Sarcoidosis and idiopathic pulmonary fibrosis are the most common ILDs of unknown etiology.

General aspects of ILD

General features of ILD are presented below. Organizing pneumonia (old name: bronchiolitis obliterans organizing pneumonia , BOOP) has a course and prognosis that differ from the other ILD. See separate paragraph on next page.

Symptoms and physical findings

Dyspnea is a common and prominent complaint in patients with ILD. Findings at physical examination are usually not specific. Most commonly, physical examination eveals tachypnea and bibasilar end-inspiratory dry crackles.

Radiology

ILD may be first suspected based on an abnormal chest radiograph, which most commonly reveals a bibasilar reticular pattern. A nodular or mixed pattern of alveolar filling and increased reticular markings may also be present. In most cases, the chest radio graph is nonspecific and usually does not allow a specific diagnosis. High-resolution CT (HRCT) is superior to the plain chest x-ray for early detection and confirmation of suspected ILD.[1]

Treatment

Since therapy does not reverse fibrosis, the major goals of treatment are permanent removal of the offending agent, when known, and early identification and aggressive suppression of the acute and chronic inflammatory process, thereby reducing further lung damage. Corticosteroids are the mainstay of therapy for suppression of the alveolitis present in ILD, but the success rate is low and there is no direct evidence that steroids improve survival. Many cases of ILD are chronic and irreversible despite the therapy and lung transplantation may then be considered.

Pneumonitis *versus* **pneumonia**

Pneumonia is a term that was used in the past for lung inflammation that resulted from infection. Pneumonitis is lung inflammation in general but was mainly used if the inflammation was not caused by infection. The terms pneumonia and pneumonitis are often used interchangeably. In recent publications on interstitial lung diseases, the term pneumonia is used, such as in lymphocytic interstitial pneumonia (LIP).

Parambil *et al* analyzed 18 patients with pSS and interstitial lung disease.[3] Most patients presented with dyspnea and cough. The most common lung diseases were nonspecific interstitial pneumonia and organizing pneumonia (table 11.1).

Patients with Sjögren's syndrome without respiratory symptoms and a normal chest x-ray, may have pulmonary abnormalities on high-resolution CT.[1]

Lung diseases in Sjögren's syndrome

The following pulmonary disorders will be discussed in relation with Sjögren's syndrome:

1. tracheitis and bronchitis
2. pleuritis
3. interstitial lung diseases
   a. nonspecific interstitial pneumonia
   b. lymphocytic interstitial pneumonia
   c. usual interstitial pneumonia
d. organizing pneumonia
4. pulmonary lymphoma
5. amyloidosis
6. blood vessel mediated disorders
   a. pulmonary embolism
   b. pulmonary arterial hypertension
   c. pulmonary vasculitis

1. Tracheitis and bronchitis

Tracheitis sicca and bronchitis sicca are inflammations of the trachea and bronchi due to dryness. Mild forms are probably very common but no data are available in the medical literature.

2. Pleuritis

Pleuritis, inflammation of the pleura, may be seen in patients with sSS and SLE or RA. It is almost nonexistent in pSS.

3. Interstitial lung disease

The most common forms of interstitial lung diseases (ILDs) in pSS patients are nonspecific interstitialpneumonia (NSIP), organizing pneumonia (OP) [2,3] and lymphocytic interstitial pneumonia (LIP).[8] Pulmonary manifestations may occasionally precede the more typical systemic manifestations ofauto immune diseases by months or years.

Uffman *et al* studied 37 consecutive patients with pSS and normal chest radiographs.[1] Abnormal HRCT findings were seen in 24 patients (65%), seven of whom had normal pulmonary function tests (PFTs). The overall correlation between HRCT and PFTs was poor. HRCT and PFTs appear to be sensitive for both the early detection of parenchymal abnormalities and a decrease in lung function in asymptomatic patients with pSS. However, abnormal HRCT findings do not necessarily indicate a substantial alteration in PFTs. ILDs in patients with pSS are associated with a variety of histopathologic patterns that appear to have therapeutic and prognostic implications. Diffuse ILD is the most serious form of lung involvement due to its potentially progressive nature and the concomitant risk of respiratory failure.[3]

Parambil *et al* performed a follow-up of 18 patients with pSS.[3] Seven patients (39%) died during the follow-up after a median interval of 67 months following the diagnosis of ILD.

3a. Nonspecific interstitial pneumonia

Nonspecific interstitial pneumonia (NSIP) is non-specific" in that it presents similarly to the other ILDs, but lacks the histopathologic features that characterize the individual disorders. On the basis of the histopathology of the alveolar wall, three groups of NSIP are distinguished. Group I shows primarily interstitial inflammation; II: inflammation and fibrosis; III: primarily fibrosis. Some patients also show areas with the histopathology of UIP (see further).

Treatment consists of corticosteroids. Azathioprine may be added as a steroid-sparing agent or in patients with no or incomplete response. Cyclophosphamide is used in patients with severe initial disease and in those who have progressed on therapy with corsticosteroids and azathioprine.[22]

The prognosis in idiopathic cases is better than in patients with a systemic autoimmune disease. Specific therapies for those diseases may guide treat ment of the NSIP.[22] The prognosis of NSIP is better than of UIP (see below).

3b. Lymphocytic interstitial pneumonia

Lymphocytic interstitial pneumonia (LIP) occurs in a wide variety of settings such as autoimmune disease (usually Sjögren's syndrome), AIDS and as an adverse reaction to medications.

The incidence of LIP is about twofold greater in women than men. Symptoms of progressive cough and dyspnea predominate. LIP is an inflammation around the small bronchial tubes in the lungs that resembles the inflammation found in the lacrimal and salivary glands.[10]

Recognition of LIP is important as it is potentially treatable. It is frequently misdiag nosed and treated as infectious pneumonia multiple times before the correct diagnosis is made. HRCT shows extensive areas of ground-glass attenuation and interlobular septal

thickening with scattered thin-walled cysts. An open-lung biopsy is the best method of diagnosing this condition, as less invasive techniques do not provide an adequate tissue specimen.

LIP is characterized by diffuse hyperplasia of bronchus-associated lymphoid tissue. The dominant microscopic feature of LIP is a diffuse, polyclonal lymphoid cell infiltrate surrounding airways and expanding the lung interstitium. LIP belongs within a spectrum of pulmonary lymphoproliferative disorders that range in severity from benign, small, airway centered cellular aggregates to malignant lymphomas.[9]

There is great variability in the clinical course of LIP, from resolution without treatment to progressive respiratory failure and death. LIP is often regarded as a steroid-responsive condition, and oral corticosteroids continue to be the mainstay of therapy, but the response is unpredictable. There have been no controlled trials to date. About 33-50% of patients die within 5 years of diagnosis, and about 5% of cases of LIP transform to lymphoma.[9]

3c. Usual interstitial pneumonia

In usual interstitial pneumonia (UIP), pulmonary function tests show a restrictive pattern and chest radiographs diffuse interstitial opacities associated with reduced lung volumes. HRCT shows a characteristic pattern of subpleural and bibasilar reticulonodular opacities with architectural distortion including honeycomb changes and traction bronchiectasis.

The histologic hallmark of UIP is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci and honeycomb change.[14] Most patients with UIP die of respiratory failure within 5-10 years.[14]

3d. Organizing pneumonia

The name BOOP (Bronchiolitis Obliterans with Organizing Pneumonia) has been replaced by "organizing pneumonia" (OP) to avoid confusion with airway diseases such as constrictive bronchiolitis obliterans.[11,15] If the cause of OP is not known, it is called *cryptogenic organizing pneumonia*. The word organizing reflects the so-called organisation of the inflammatory exudates. The sequence of events is:

1. initial alveolar epithelial injury and infiltration of the alveolar interstitium with lymphocytes and neutrophils; the organisation is characterised by intraalveolar formation of fibrinoid inflammatory cell clusters
2. the formation of fibroinflammatory buds; fibroblasts become myofibroblasts and re-epithelialisation occurs by progressive proliferation of alveolar cells
3. the inflammatory cells disappear almost completely from most buds.

The organisation has many similarities with the process of normal wound healing.[16] The end result may be resolution of the inflammation or fibrosis.

Disease presentation

Patients typically present with an illness of short duration, usually less than 3 months, with variable degrees of cough and dyspnea. The cough may be productive of clear or discolored sputum. Symptoms usually follow a suspected but unconfirmed lower respiratory tract infection, and patients have often received at least one and frequently several courses of antibiotics.

Diagnosis

The diagnosis depends on finding the characteristic pathologoical features of the disease in the proper clinical setting.[17] In one-half of the cases, the onset is heralded by a flu-like illness with fever, malaise, fatigue, and cough. The most common features at presentation are persistent nonproductive cough, dyspnea with exertion and weight loss.

Lung function tests confirm a restrictive ventilatory pattern (usually mild to moderate) with a moderately reduced diffusion capacity in most. Localized or more widespread crackles are frequently present. A markedly raised ESR, elevated CRP, and increased blood neutrophilis are common findings.[11]

The chest x-ray is quite distinctive, with bilateral diffuse alveolar opacities in the presence og normal lung volumes.

Examples of diseases that should be excluded are bacterial pneumonia, hypersensitivity pneumonitis, chronic eosinophilc pneumonia and pulmonary drug reactions.

Treatment and prognosis

The majority of patients recover completely on administration of oral corticosteroids, but a significant number relapse within 1-3 months when the corticosteroids are reduced (usually to below 15 mg/d) or stopped. Prolonged treatment for 6 months or longer is advised. A small proportion of patients recovers spontaneously. Rare cases progress to respiratory failure and death.[11] Organizing pneumonitis in systemic

autoimmune diseases usually runs a more severe course and need immunosuppressive treatment in addition to corticosteroids.

4. Pulmonary lymphoma

Pulmonary lymphoma in Sjögren's syndrome usually is a MALT-lymphoma, a lymphoma of mucosaassociated lymphoid tissue. Pulmonary lymphoma may occur within the spectrum of lymphocytic interstitial pneumonia (see back), a spectrum of pulmonary lymphoproliferative disorders that range in severity from benign, small, airway-centered polyclonal cellular aggregates to monoclonal malignant lymphomas.[9]

5. Pulmonary amyloidosis

Amyloidosis is a term that refers to the tissue deposition of fibrils of a variety of proteins. Amyloid deposition can be isolated to a single organ (*e.g.* Alzheimer's disease) or occur in many organs, the major sites being kidneys, heart and liver. Several types of amyloidosis are hereditary or secondary to chronic inflammatory diseases.[19]

In secondary amyloidosis, the fibrils are composed of fragments of serum amyloid A (SAA), an acute phase reactant. Underlying disorders are rheumatoid arthritis in one-half of the cases and further ankylosing spondylitis, familial Mediterranean fever, psoriatic arthritis and Crohn's disease.[19] Secondary amyloidosis can be expected to occur mainly in sSS patients with longstanding active rheumatoid arthritis. Very few case reports have been published on secondary amyloidosis in pSS. The best documented paper is from Ooms *et al.*[20] She described the case of a 53-year-old man with pSS according to the American-European criteria complicated by longstanding chronic interstitial nephritis.

The patient was negative for ANA, antibodies to SSA/Ro and SSB/La and rheumatoid factor. Other laboratory tests revealed strongly elevated ESR and CRP as well as a mild polyclonal hypergammaglobulinemia. The amyloid deposition in the kidneys caused renal failure and nephrotic syndrome.

Wong *et al* described a 29-year-old woman who presented with diffuse pulmonary nodular amyloidosis and was subsequently diagnosed as having Sjögren's syndrome.[21]

It may be concluded that secondary amyloidosis can occur in patients with Sjögren's syndrome and another disease with severe inflammation. However, the finding of secondary amyloidosis in a pSS patient warrants a very careful search for an underlying inflammatory disease as the cause of secondary amyloidosis other than pSS.

6. Blood vessel mediated disorders

6a. Pulmonary embolism

Pulmonary embolism (PE) is a major cause of death and may occur without or with a relationship with Sjögren's syndrome. A related cause mainly concerns the antiphospholipid syndrome (APS). APS is caused by autoanti bodies against phospholipid- associated molecules and may cause thrombosis in both veins and arteries. When venous thrombi dislodge from their site of formation, they embolize to the pulmonary arterial circulation or, paradoxically, to the arterial circulation through a patent foramen ovale or atrial septal defect. About half of patients with pelvic vein thrombosis or proximal leg deep venous thrombosis (DVT) develop PE, which is usually asymptomatic. Isolated calf vein thrombi pose a much lower risk of PE, but they are the most common source of paradoxical embolism.

Acquired predispositions for thromboembolism are much more relevant than genetic factors and include long air travel, obesity, cigarette smoking, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, trauma, and medical conditions such as antiphospholipid syndrome, cancer, systemic arterial hypertension, and chronic obstructive pulmonary disease.

PE results in gas exchange abnormalities such as hypoxemia and other pathophysiological abnormalities including increased pulmonary vascular resistance. Progressive right heart failure is the usual cause of death from PE.

6b. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries with vascular proliferation and remodeling, resulting in a progressive increase in pulmonary vascular resistance and right ventricular heart failure. Right-heart catheterization is the gold standard for the diagnosis.

PSS patients with PAH had Raynaud phenomenon, cutaneous vasculitis, and interstitial lung disease significantly more frequently than pSS without PAH. They also more frequently had ANA, a positive rheumatoid factor, autoantibodies to SSA/Ro and RNP, as well as hypergammaglobulinemia. These data suggest that systemic vasculopathy, B cell activation, and autoimmunity could play a role in the pathophysiology of Sjögren-associated PAH.

Launay *et al* [6] discussed whether PAH is truly a complication of primary Sjögren's syndrome or if the association could be fortuitous in patients displaying idiopathic PAH or other causes of pulmonary hypertension. Many data favor a true link be-

tween PAH and pSS. First, PAH occurred most often in Sjögrenpatients with laboratory markers of intense B-cell activation, such as a high frequency of antinuclear antibodies and hypergammaglobulinemia. Second, immunofluorescence studies revealed deposits immunoglobulins and complement in the pulmonary arteriolar walls of patients with Sjögren-associated PAH. Third, PAH in these Sjögren patients sometimes responds favorably to immunosuppressive therapy alone, which is not the case in idiopathic PAH.

Although rare, PAH should be searched for promptly in patients with pSS with unexplained dyspnea, in order to establish the diagnosis sooner, with presumably a better prognosis.

PAH has a poor prognosis but treatment options have progressed strikingly in recent years. As B-cells activation and antibodies formation are thought to play a role in the pathophysiology of Sjögren-associated PAH, anti-CD 20 (*e.g.* rituximab) could be a therapeutic option in the future.[6]

6c. Pulmonary vasculitis

Pulmonary vasculitis (PV) is a common finding in a number of uncommon disease entities and may be a part of a systemic vasculitis or the sole site of involvement.

PV is characterized pathologically by cellular inflammation, destruction of the blood vessel wall, and tissue necrosis.

Clinically, PV is characterized by the size, type, and location of the affected vessels in association with the degree of inflammation, vessel destruction,and tissue necrosis.

PV is a common feature of Wegener's granulomatosis and Churg-Strauss syndrome. It may also occur in systemic autoimmune diseases such as RA, SLE, derma tomyositis and systemic sclerosis.[18] It may, therefore, also be seen in patients with these diseases in combination with secondary SS.

Publications on clinically relevant cases of PV in pSS could not be found.

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Urogenital disorders 12

In this chapter, five urogenital disorders are discussed that occur more often in patients with Sjögren's syndrome than in the general population. These disorders are:

1. overactive bladder syndrome
2. interstitial cystitis/bladder pain syndrome
3. non-bacterial prostatitis
4. vulvodynia
5. dyspareunia

1. Overactive bladder syndrome

Overactive bladder (OAB) syndrome is the term used to describe the symptom complex of urinary *urgency* with or without urge *incontinence*, usually with *frequency* and *nocturia*, in the absence of any sign of infection or other identifiable cause of the symptoms.[36] Symptoms of overactive bladder may also have identifiable causes

OAB with incontinence is currently referred to as *OAB wet*, in contrast to *OAB dry* when there is no incontinence.

The symptoms of OAB are primarily due to involuntary contractions of the *detrusor* muscle during the filling phase of the micturition cycle. These contractions, when observed during urodynamic studies, are termed *detrusor overactivity* and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors.[38]

OAB symptoms have a profound impact on the quality of life and patients may feel a sense of shame and embarrassment, in particular in OAB wet.[9]

The diagnosis of OAB is based on symptoms and does not require invasive tests. Careful questioning about symptoms is important in achieving a differential diagnosis (table 12.2). The most common differential diagnosis is a urinary tract infection but in a small number of cases bladder cancer is underlying the symptoms of OAB.

OAB and IC/BPS

overactive bladder syndrome
- no pain, pressure or discomfort perceived to be related to the urinary bladder
- with or without urge incontinence

interstitial cystitis / bladder pain syndrome
- always pain, pressure or discomfort perceived to be related to the urinary bladder
- incontinence is not a symptom of the disease

Table 12.1 Examples of causes of overactive bladder symptoms

- detrusor overactivity (overactive bladder syndrome, OAB)
- urinary tract infections
- drugs (side-effects)
- bladder cancer; prostate cancer
- benign prostatic hyperplasia
- stones in the bladder
- constipation
- pelvic organ prolapse
- bladder injury
- nerve damage
- neurological diseases (multiple sclerosis, Parkinson's disease, spinal cord lesions, spina bifida, stroke)

Table 12.2 Presenting symptomatology for overactive bladder (OAB), bladder cancer and urinary tract infections (UTIs) [9]

presenting symptom	*OAB*	*bladder cancer*	*UTI*
urgency	yes	occasionally	yes
frequency	yes	occasionally	yes
urgency incontinence	33%	occasionally	occasionally
nocturnal frequency	often	rare	often
pain	no	occasionally	yes
dysuria	no	occasionally	yes
pyuria	no	rare	yes
haematuria	no	yes	usually microscopic

Urinary incontinence

The *National Institute for Health and Clinical Excellence* has recently published guidelines on the management of urinary incontinence in women.[39] The guidelines are summarised below:

Assessment and investigation
At initial clinical assessment, incontinence should be categorised based on the patient's symptoms and treatment should be directed towards the predominant symptom. A bladder diary should be used in the initial assessment. The use of urodynamics is not recommended before conservative treatment.

Conservative management
Bladder training for a minimum of 6 weeks should be offered as first line treatment.

Drug treatment
Immediate release non-proprietary oxybutynin should be offered as first line drug treatment if bladder training has been ineffective. If this is not well tolerated, darifenacin, solifenacin, tolterodine, trospium or an extended release or transdermal formulation of oxybutynin should be considered as alternatives. Women should be counselled about the side effects of
antimuscarinic drugs.

Surgical management
Sacral nerve stimulation is recommended for women who have detrusor overactivity not responsive to conservative or medical treatment.

Competence of surgeons performing operative procedures for incontinence in women
Surgery for incontinence should only be undertaken by surgeons who have received appropriate training in the management of incontinence and associated disorders or who work within a multidisciplinary team with this training and who regularly carry out this form of surgery.

Treatment of OAB includes bladder training, diet modification, drugs, neuromodulation and in the last resort surgery. Anticholinergic drugs are the mainstay of drug treatment for OAB symptoms but have side-effects such as dry mouth and dry eyes. Intravesical injections of botulinum toxin A (Botox A) into the detrusor muscle and/or bladder sphincter have produced good results for OAB that failed to respond to other treatments.

See box above for various aspects of urinary incontinence.

OAB and Sjögren's syndrome

Walker *et al* [41] found that 61% of patients with primary Sjögren's syndrome reported severe urological symptoms compared with 40% of control patients with osteoarthritis. This difference was predominantly attributable to bladder irritability associated with urgency and not nocturia (OAB).

Cause of OAB in Sjögren's syndrome

Wang *et al* [40] did an interesting study on the passive transfer of serum IgG from patients with Sjögren's syndrome. The IgG showed inhibitory anti-muscarinic M3 receptor (M3R) activity but produced a paradoxical increase in contractile responses of detrusor strips to cholinergic stimulation. Cystometry of whole bladders revealed a corresponding decrease in bladder wall compliance and phasic detrusor contractions upon filling, replicating the urodynamic features of overactive bladder. The features of cholinergic hyper-responsiveness were associated with increased post-synaptic M3R expression and were reproduced by injecting mice with a rabbit antibody against the second extracellular loop of M3R. These findings were consistent with the notion that there was initial inhibition of parasympathetic neurotransmission by antagonistic autoantibodies to M3R, which produced a compensatory increase in M3R expression *in vivo*. The enhanced cholinergic responses during bladder distention resulted in detrusor overactivity.

These data suggest that the overactive bladder associated with Sjögren's syndrome is an autoantibody-mediated disorder of the autonomic nervous system, which may be part of a wider spectrum of cholinergic hyperresponsiveness.[40]

2. Interstitial cystitis/bladder pain syndrome

Interstitial cystitis or *bladder pain syndrome* (IC/BPS) is a chronic bladder disease characterized by symptoms of cystitis. These are pain, pressure or discomfort in or around the bladder, a persistent urge to urinate and frequent urination both in the daytime and at night. The pain usually increases as the bladder fills. However, no urinary tract infection can be found. The symptoms have serious consequences for the social and personal life of the patients. In the case of many patients, it may take many years before the diagnosis of IC/BPS is established.

During the past few years, there has been much international discussion concerning the name and definition of this disease. Other names that are used are painful bladder syndrome (PBS) or hypersensitive bladder, with or without the addition of IC.

Definition of the disease

The name interstitial cystitis suggests that inflammation is present in the interstitium of the bladder. A great problem was that in many patients with varying degrees of chronic urinary symptoms and pelvic pain, no abnormalities could be found by physical, microbiological and histological investigations.[63,64] The inability to make a classifying diagnosis in these patients necessitated resolving the discrepancies between nomenclature, definitions and clinical practice by introducing other names, definitions and diagnostic criteria.

In 1987, Holm-Bentzen expanded the concept of interstitial cystitis by describing it as a subgroup of *painful bladder disease* with abnormal findings such as detrusor mastocytosis.[65]

In 1988, the NIDDK (National Institute for Diabetes and Digestive and Kidney Diseases) consensus criteria for the research diagnosis of interstitial cystitis (IC) were published.[61] These so-called NIDDK criteria did not require histological evidence of inflammation. The NIDDK criteria were found to be very specific, but more than 60% of patients regarded by researchers as definitely or likely to have IC did not fulfil the NIDDK criteria.[62]

In 1989, Witherow *et al* used the name *painful bladder syndrome* (PBS), defined as a clinical diagnosis in patients with symptoms of varying severity.[66] These symptoms always included frequency and suprapubic pain and occasionally dysuria, nocturia and urgency persisting for more than 3 months with no loss of bladder capacity and no overt infection. The term PBS was used independently of objective bladder pathology.

In 2002, the International Continence Society (ICS) defined PBS as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology.[67] In a footnote it is stated that "The ICS believes this to be a preferable term to interstitial cystitis. Interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features. In the investigation of bladder pain it may be necessary to exclude conditions such as carcinoma *in situ* and endometriosis".

The Chronic Pelvic Pain Group of the European Association of Urology (EAU) expanded the concept in a classification based on chronic pain, the perceived localization of the pain and possible abnormal findings.[68] Chronic pelvic pain was defined as non-malignant pain perceived in structures related to the pelvis. Chronic pelvic pain syndrome was described as the occurrence of persistent or recurrent episodic pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction, without proven infection or other obvious pathology.[68] The EAU definitions use the axial structure of the International Association for the Study of Pain (IASP; www.iasp-pain.org) and as symptoms invariably define the clinical condition, they consider the term *painful bladder syndrome* or *bladder pain syndrome* more apposite.[68] The EAU Group clearly distinguishes classic ulcer disease from non-ulcer bladder pain syndrome. They state that these can be discriminated non-invasively and show different clinical presentations, age distributions, histopathology, response to treatment and clinical course. Depending on the level of available evidence, classification of a particular patient may change over time, *e.g.* from chronic pelvic pain syndrome to bladder pain syndrome or interstitial cystitis.

In 2004, the International Scientific Committee at the 3rd International Consultation on Incontinence (ICI) gave the following recommendation on what kind of patient should be evaluated for PBS/IC.[69] "Men or women with bladder pain, with or without a sensation of urgency, often with urinary frequency and nocturia (especially if drinking a normal amount of fluids) and no abnormal gynecologic findings to explain the symptoms should be evaluated for PBS/IC. Patients with infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and haematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with PBS/IC."

The European Society for the Study of IC/PBS (ESSIC; www.essic.eu) presented their consensus on definitions, confusable diseases, diagnostic criteria, disease types and a proposal to change the name into bladder pain syndrome (BPS) at a NIDDK meeting in October 2006 (www.niddk.nih.gov/fund/other/niddkfrontiers/frontiers in PBS Summary report.pdf). Their proposed diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis was published in 2008.[33] In short, it was concluded that "the diagnosis will be made on the basis of the symptom of chronic pain related to the urinary bladder, accompanied by at least one other urinary symptom such as daytime and night-time frequency, exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistension and biopsy if indicated."

In a reaction to these proposals, the Association of Reproductive Health Professionals (ARHP) held a multidisciplinary meeting of researchers, clinicians and patients in the USA in February 2007.[86] In a majority statement, IC/PBS was defined as follows: "Pelvic pain, pressure, or discomfort related to the bladder, typically associated with persistent urge or urinary frequency, in the absence of infection or other pathology."

At the 2nd International Consultation on Interstitial Cystitis Japan (ICICJ) in March 2007, Homma proposed the term hypersensitive bladder syndrome (HSB) characterized by increased sensation, usually associated with frequency and urgency, with or without bladder pain. PBS is defined as a symptom syndrome characterized by bladder pain, usually associated with frequency, urgency and increased sensation. IC is defined as a disease name that should not be used as a symptom syndrome. IC is characterized by 1. HSB; 2. no other obvious diseases that explain the HSB, and 3. bladder pathology (histological evidence of inflammation and/or abnormal cystoscopic findings (Hunner's ulcer or bladder bleeding at hydrodistension). PBS is contained in the HSB, while IC is also contained in HSB, but only partially overlaps PBS and OAB, meaning that some patients with IC have neither urgency nor pain.

Pain

It can be concluded that there is strong international support (ICS, EAU, IASP, ICI, ARHP, ESSIC) to consider pain as a key feature of PBS/IC while urgency and frequency are common symptoms but not a prerequisite for a diagnosis.

See paragraph on definition of the disease

It can be concluded that there is strong international support (ICS, EAU, IASP, ICI, ARHP, ESSIC) to consider pain as a key feature of PBS/IC while urgency and frequency are common symptoms but not a prerequisite for a diagnosis (table 12.3).

Table 12.3 Summary of the mandatory features for the diagnosis of IC/BPS as proposed by various authors and scientific organizations. See the text for explanation of the abbreviations.

SOURCE	DISEASE NAME	PAIN	URGENCY	FREQUENCY	
Holm-Bentzen [65]	IC is subgroup of PB disease	yes?	no	no	
NIDDK [61]	IC	pain *or* urgency		no	pain or urgency; glomerulations or Hunner's "ulcer"
Witherow [66]	PBS	yes	no	yes	
ICS [67]	PBS IC	yes yes	no no	no no	IC=PBS + cystoscopic and histological features
EAU [68]	PBS/BPS	yes	no	no	
ICI [69]	PBS/IC	yes	no	no	
ESSIC [33]	BPS types	yes	no	no	
ARHP [86]	IC/PBS	yes	urgency *or* frequency		
Homma (ICICJ 2007)	HSB PBS IC	no yes no	no no no	no no no	

ESSIC has slightly adapted its initial disease description on the basis of the discussions at the ARHP and 2nd ICICJ meetings (see below).

ESSIC diagnostic criteria

The *European Society for the Study of IC/PBS* (ESSIC) has recently proposed a new definition, new diagnostic criteria and the name bladder pain syndrome (BPS).[33] ESSIC has defined types of BPS on the basis of findings used to document the diagnosis of BPS.

BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate increasing grade of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate increasing grade of abnormality of biopsy findings. X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done (see figure 12.1).

The name IC/BPS will be used here further as a synonym for interstitial cystitis, painful bladder syndrome and bladder pain syndrome.

Pain, pressure and discomfort

Many patients report a sensation of pressure or discomfort in the bladder/pelvic area and do not report this sensation as pain but rather as urgency.

The IASP (*International Association for the Study of Pain*; www.iasp-pain.org) definition of pain is:
"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Patients having microwave treatment for benign prostatic obstruction producing tissue damage at the bladder neck report the same sensation of pressure and discomfort in the bladder region. The sensation is therefore by definition a pain sensation, but not described as such by the patient.[33]

> The sensations of pressure and/or discomfort in the bladder/pelvic area are by definition pain sensations.
>
> *ESSIC* [33]

Disease characteristics

Cystoscopy is an essential diagnostic procedure for IC/BPS because it allows the inside of the bladder to be examined and small samples of tissue to be taken. This enables many other diseases such as *carcinoma in situ* to be excluded as a cause of the symptoms. A number of findings are considered to be hallmarks of IC/BPS, despite not being specific. These are glomerulations (diffuse pinpoint haemorrhages) in the bladder wall when the bladder is filled with water, a bladder capacity of less than 350 ml and so-called Hunner's "ulcers". None of these characteristics are found in all patients.

The typical histological finding in IC/BPS is submucosal edema, vasodilatation and an inflammatory infiltrate of lymphocytes and mast cells.[2] The number of mast cells is particularly elevated in the detrusor muscle layer and to a lesser extent in the mucosa and submucosa.[3] Immunofluorescence may show

		CYSTOSCOPY WITH HYDRODISTENSION			
		not done	normal	glomerulations [1]	Hunner's lesion [2]
BIOPSY	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive [3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade II-III
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Figure 12.1 *BPS types as proposed by the European Society for the Study of IC/PBS (ESSIC).* [33] *BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate grades of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate grades of abnormality of biopsy findings.*[34] *X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done.*

ESSIC definition of Bladder Pain Syndrome [33]

ESSIC agreed that BPS would be diagnosed on the basis of chronic* pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency.

Confusable diseases as the cause of the symptoms must be excluded.

Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies.

The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.

* chronic: > 6 months
ESSIC: http://www.essic.eu

Comment

If, in a rare situation, a patient fulfills the definition of BPS but the duration of the symptoms is less than 6 months, a clinical diagnosis of BPS should be made anyhow; it would only have implications if the patient is screened for participation in a scientific study: the short duration can be mentioned or the patient should be excluded from the study.

strong diffuse or focal colouring of IgA throughout the urothelium. IgE can sometimes be seen on mast cells.[4] In some patients the bladder is fibrotic.

Hunner's lesion (Hunner's "ulcer")

Hunner's lesion or Hunner's "ulcer" is a distinctive inflammatory lesion presenting a characteristic deep rupture through the mucosa and submucosa provoked by bladder distension. Despite the name, it is not an ulcer. ESSIC, therefore, has decided to use the name *Hunner's lesion* instead of Hunner's ulcer.[33] The detection of Hunner's lesions is in general only possible at cystoscopy with hydrodistension under proper anesthesia by an experienced urologist with training to detect them.

Definition of Hunner's lesion

The following definition by Magnus Fall was accepted by ESSIC: [33]

The Hunner's lesion typically presents as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.

Classic IC

IC with Hunner's lesions is called *classic IC* as opposed to *nonulcer IC* when Hunner's lesions are not found. Classic IC is the same as BPS type 3A, 3B or 3C depending on whether biopsies were done and, if so, the biopsy findings.

It is not clear to date whether the nonulcer and classic types represent different stages of a single disease, or whether they are different disease entities. Patients with the nonulcer type are 10 years younger on average than those with the classic type but this is compatible with both theories. The lack of data that patients with nonulcer type progress to the classic type is in line with the hypothesis that they represent different diseases. However, several circumstances severely hamper the detection of such transitions in clinical practice. These are:

1. the chance to detect Hunner's lesions are directly related to the urologists' experience; these skills are likely to be concentrated in particular urological centres;

2. the detection of Hunner's lesions usually requires cystoscopy with hydrodistension;

3. Hunner's lesions tend to recur and have likely been already present before their first detection.

This implies that if an existing Hunner's lesion is not detected (missed) at the first clinical evaluation, it will not be detected later either. But if the initial evaluation correctly did not reveal a Hunner's lesion, a newly developed Hunner's lesion is likely to be missed. This makes it almost impossible to document transitions from nonulcer type into classical type. Future studies, in which patients are evaluated and classified according to the ESSIC guidelines,[33,34] are needed to clarify this issue. The measurement of the nitric oxide (NO) concentration in the bladder lumen may be an important aid for the early detection of

Hunner's lesions (see below).

Nitric oxide in the bladder lumen
Logadottir *et al* found that all their IC/BPS patients with Hunner's lesions had high levels of luminal nitric oxide (NO) while none of the other patients had any significant increase in NO levels in the bladder.[85] Bacterial cystitis may also increase the NO level and must be excluded. The NO level in patients with Hunner's lesions was not related to symptoms, but rather to the assignment to this specific subgroup.

The excellent correlation between luminal NO and the presence of Hunner's lesions warrants further evaluation of the value of luminal NO measurement for the diagnosis of IC/BPS and the assessment of disease damage of IC/BPS. Moreover, NO measurement during cystoscopy without hydrodistension could be useful for selection of patients during followup that have developed new Hunner's lesions and need treatment for them.

Prevalence of Hunner's lesion
In urologic centers with expert skills to detect Hunner's lesions, Hunner's lesions are detected in about 50% of the patients with IC/BPS. The majority of IC/BPS patients with Hunner's lesions, however, are probably not recognized in centers with less experience. This underdiagnosis is probably due to a combination of factors such as:

1. the confusion caused by the name Hunner's ulcer while it is not an ulcer: the term Hunner's ulcer suggests that it can be seen at cystoscopy without hydrodistension;

2. the detection of Hunner's lesions is almost impossible if cystoscopy is performed without hydrodistension;

3. many urologists suppose that Hunner's lesions are rare; the fact that they rarely detect them is considered to be in line with this false impression;

4. even when cystoscopy with hydrodistension is performed, Hunner's lesions are likely to be detected only by experienced urologists; biopsy may be necessary to prove that it is a Hunner's lesion and/or to exclude a *carcinoma in situ*.

Treatment of Hunner's lesion
Bladder pain may improve dramatically when the Hunner's lesions are treated by electrocoagulation, laser or resection. Unfortunately, Hunner's lesions tend to recur but the interval may vary between several months and *e.g.* more than 5 years.

Prevalence of IC/BPS
IC/BPS occurs 5-10 times more frequently in women than in men. Prevalence differs per study, in part due to the use of different definitions. In the Netherlands, prevalence is estimated at 8-16 cases per 100,000 women.[5] Recently, however, far higher figures were found in the USA: varying from 197 cases per 100,000 women and 41 per 100,000 men to 10% of third year women medical students.[6-7] IC/BPS is also found in children.[8] Due to the fact that the NIDDK criteria (National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Bethesda, MD, USA) exclude the diagnosis of IC in persons under the age of 18 years, there are no figures in the literature concerning the prevalence of IC/BPS in children.

Pathogenesis and etiology
There are various theories concerning the cause of IC/BPS, none of which have been scientifically proven. It is consequently often suggested that IC/BPS may be multicausal. A number of these theories will be briefly discussed below.

Increased permeability of the bladder mucosa
The bladder wall is covered with a mucin layer which includes glyclosaminoglycans (GAGs). GAGs are hydrophilic and maintain a stable layer of water between the urothelium and bladder lumen. The theory is that a defect in the GAG causes inflammation of the urothelium through contact with bacteria and toxic agents in the urine. This hypothesis is the rationale for treating IC/BPS with drugs aimed at replacing the GAG layer, such as pentosan polysulfate, heparin, hyaluronic acid and glucosamines.

The potassium sensitivity test (PST) is based on the hypothesis that instilled potassium provokes symptoms such as pain and urgency in case of a permeable bladder epithelium. The PST has been found positive in 66-83% of patients with IC/BPS but also in similar proportions of patients with cystitis due to radiation and other causes, prostatitis, bladder cancer and even in one third of healthy subjects.[70-74] The low sensitivity and specificity makes the PST unsuitable as a diagnostic tool[75] on the one hand, and contradicts a central role of increased bladder permeability in the pathogenesis of IC/BPS on the other.

Mast cells
Detrusor mastocytosis is defined as more than 28 mast

cells per mm^2 tissue; fewer than 20 are considered to be normal.[6] While there is no correlation between the number of mast cells and the severity of the symptoms, there is a correlation, however, with the degree of inflammation in the submucosa and the presence of "ulcers".[10] Most of the mast cells are degranulated due to IgE or other isotypes binding to their Fc receptors. The vasoactive and proinflammatory mediators hereby released, such as histamine, prostaglandins, leuko- trienes and tryptases, may possibly play a role in the pathogenesis. The urine may contain elevated concentrations of methylhistamine and tryptase.

Mast cells can also release mediators without degranulation under the influence of anaphylatoxins, neuropeptides and cytokines.[11] In patients with spina bifida and fibrosis of the bladder, it has been shown that mast cells stimulate the synthesis of collagen, leading to fibrosis.[12]

Mast cells also occur in the bladder wall in healthy people and in people with bacterial cystitis and bladder carcinoma, albeit in lower numbers.[13,14] There is no consensus concerning the significance of mast cells in the bladder in IC/BPS.

Neurogenic factors

The presence of degranulated mast cells at nerve endings has led to the hypothesis of neurogenic inflammation.[15] It is believed that stimulation of sensory nerves could lead to the release of neuropeptides and mediators from mast cells. This concept could explain inflammation limited to the bladder without direct damage to or infection of the bladder.[16]

It has been demonstrated that mast cells in the bladders of mice can only provoke antigen-induced inflammation in the presence of neurokinin-1.[17]

Infection

One condition for the diagnosis of IC/BPS is the exclusion of any urinary tract infection. However, certain bacteria such as *Ureaplasma urealyticum* and *Mycoplasma hominis* require special culture methods and are therefore easily missed. There are various publications on the positive effects of antibiotics in some IC/BPS patients.[18,19] A possible role of bacteria in initiating and perpetuating IC/BPS cannot be entirely excluded since the relationship between diseases and microorganisms is a complex one, for example because the consequence of an infection depends on the genetic properties of individuals.

Toxins in the urine

In some patients, bladder symptoms may improve following surgical diversion of urine so that the urine no longer enters the bladder. This has led to the theory that the urine of IC/BPS patients contains toxic substances that cause inflammation. Support has been found for this hypothesis in animal experiments.[20] The improvement after urinary diversion could also be due to the absence of the mechanical effects of bladder volume changes due to filling and emptying of the bladder.

Urinary markers

The antiproliferative factor (APF) is a peptide secreted by bladder epithelial cells from patients with IC/BPS.[76] APF inhibits bladder cell proliferation by means of regulation of cell adhesion protein and growth factor production. It has been detected in 86% of women with IC/BPS, compared with 8% of asymptomatic control women, 12% of women with bacterial cystitis, and 0% of women with vulvovaginitis, yielding sensitivity and specificity values of 91.4% and 90.6%, respectively. The test is advocated as a useful noninvasive means for diagnosing IC/BPS in women.[21,77] However, no data on the clinical value of the APF test for the diagnosis of IC/BPS are available to support this claim. Moreover, the test is not yet widely available, so it cannot be recommended as a diagnostic tool to date.

Erickson *et al* measured several urine markers in 24-hour specimens from IC/BPS patients and healthy age-matched controls.[79] Certain markers were significantly increased in IC/BPS, including APF, epidermal growth factor (EGF), insulin-like growth factor (IGF) binding protein-3 and IL-6. Markers significantly decreased in IC/BPS were heparin-binding EGF-like growth factor, cyclic guanosine monophosphate and methylhistamine. Other markers were not significantly different in the IC/BPS and control groups, including total glycosaminoglycans, epitectin, hyaluronic acid, IL-8, IL-1 and nitrates plus nitrites. Of all markers studied, APF had the least overlap in IC/BPS and control groups. The only significant association of marker with symptom score was a positive correlation of IL-6 with nocturia.

Lamale *et al* examined histamine, methylhistamine (MH), and IL-6 in the 24-hr urine of IC/BPS patients and healthy controls.[80] IL-6 and histamine levels were significantly higher in IC/BPS patients than in the controls. MH levels were also higher in IC/BPS patients, but the results were not statistically significant. Of these three markers, no marker alone was able to distinguish as effectively between the patient and the control group.

Boucher *et al* investigated the number of tryptase positive bladder mast cells and the level of urine tryptase in IC/BPS patients.[81] Tryptase was measured in

urine samples collected immediately (spot) and during a period of 24 hours. The patients' spot urine sample tryptase levels were indistinguishable from those of controls. However, the tryptase levels in 24-hour urine samples were greatly elevated only in patients with IC/BPS.

Okragly *et al* found higher tryptase levels in urine samples of IC/BPS and bladder cancer patients compared to controls.[82] Histological evaluation of tissue from bladder cancer patients confirmed the presence of numerous and degranulated mast cells releasing tryptase into the milieu. This finding suggests that urinary tryptase levels correlate with mast cell degranulation occurring in the bladder.

El-Mansoury *et al* found that in IC/BPS patients the histamine levels were slightly increased in the spot and 24-hour urine collections.[83] MH, on the other hand, a major metabolite of histamine, was greatly elevated in spot and 24-hour urine samples.

Erickson *et al* did not find significant associations between urine MH and symptom scores, response to bladder distension, cystoscopic findings or bladder biopsy features, including mast cell count by tryptase staining.[84]

Studies comparing several urinary markers between IC/BPS patients and healthy controls failed to show that urinary markers are useful for discrimination between these groups. But even if parameters that could distinguish IC/BPS patients from healthy subjects were found, these were not of much interest as the distinction between IC/BPS patients and healthy subjects is never a relevant clinical question in patient care. More interesting is the question whether urinary markers correlate with disease activity, disease damage or long-term prognosis in individual patients when measured longitudinally. No such markers have been found to date.

Nitric oxide

See back under Hunner's lesions for further information on nitric oxice in the bladder lumen.

Phenylacetylglutamine

Fukui *et al* analyzed urine samples from 10 patients with BPS/IC, 10 with bacterial cystitis and 10 healthy subjects using a non-targeted quantitative analysis of tissue and bio-fluids for low molecular mass organic endogenous metabolites.[78] A urinary marker of IC/BPS was identified as phenylacetylglutamine (PAGN). The urinary level of PAGN measured relative to creatinine (Cr) was significantly elevated in IC/BPS patients (mean 0.47mg/mg Cr) compared with bacterial cystitis patients (mean 0.25mg/mg Cr) and healthy subjects (mean 0.11mg/mg Cr). Urinary PAGN/Cr ratios in patients with mild and moderate IC/BPS were higher than for patients with severe IC/BPS.

PAGN is a normal constituent of human urine and is formed in the liver from the condensation of glutamine with phenylacetyl-CoA. Urinary levels may be influenced by medications and/or ingestion of materials with a structure similar to that of phenylalanine. The sweetener aspartame, which contains phenylalanine in its structure, may be metabolized to PAGN. PAGN detected in this study was considered to not have been influenced by medication and/or food, because of the analyzed urine specimens were collected in the morning before medication and/or breakfast.

The reason for IC patients excreting increased PAGN into their urine is not clear. The investigators suggest that urinary PAGN/Cr ratio is a potential marker of IC and that it may indicate an underlying pathological condition in early IC patients, *e.g.* an abnormal amino acid metabolism.

This is an interesting finding but awaits confirmation in larger patient populations and the reproduction in other laboratoria around the world.

Genetic factors

In a study with 8 monozygote twins and 26 dizygote twins, concordance was found in the monozygote twins varying from 37.5% (confirmed IC/BPS in the co-twin) to 62.5% (probable IC/BPS in the co-twin). In the dizygote twins, concordance was 0%.[22]

The prevalence of IC/BPS among first-degree relatives (parent, brother, sister, or child) of patients with IC/BPS was subsequently compared with the prevalence of IC/BPS in the general population.[43] It was found that adult female first-degree relatives of patients with IC/BPS may have a prevalence of IC/BPS 17 times that found in the general population. This, together with the previously reported evidence showing a greater concordance of IC/BPS among monozygotic than dizygotic twins, suggests a genetic susceptibility to IC/BPS.

Association of IC/BPS with other diseases

IC/BPS often occurs in association with other diseases (table 12.4). This concerns allergies, fibromyalgia, irritable bowel syndrome, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome.

Allergy

In a survey study in the United States, 40.6 % of the patients with IC/BPS stated that they suffered from allergy and in a Swedish study 41-47%.[23,24] In a Japanese study, young IC/BPS patients (20-39 years) were studied in more detail and compared with an older IC/BPS group (50-69 years). The study looked at the number of allergies, the type of IC/BPS symptoms ("painful type" or "frequency and urgency type"), skin tests, blood tests and the course of the IC/BPS following hydrodistension.[25] In two patients from the young group, IC/BPS was considered to be part of generalised allergic diseases. In 25 patients an association was assumed between IC/BPS and the allergy and in 15 of these the symptoms of allergy and IC/BPS alternated or ran parallel. Eleven patients had multiple allergies. In the young patients, 86% had one or more allergies, in the older patients this was 19%.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a disorder of the function of the intestines and not an inflammatory condition. In questionnaires, 25-43% of IC/BPS patients mentioned they had IBS, 2-4x more than the normal prevalence.[23,35]

IBS is clinically important as abdominal bloating may be responsible for pressure on the stomach (dyspepsia) and bladder. Inflammation is not part of IBS and this is a marked difference with IC/BPS. Further information can be found in the chapter on gastrointestinal disorders.

Fibromyalgia

Fibromyalgia occurs in 3% of the population and more commonly in women than in men. The main symptom is pain all over the body, followed by fatigue, morning stiffness and sleep disturbances. In the USA survey 12.8% of IC/BPS patients stated that they suffered from fibromyalgia, 4x more frequent than in the general population.[23] See the chapter on fibromyalgia for further information.

Crohn's disease and ulcerative colitis

Crohn's disease and ulcerative colitis are inflammatory bowel diseases of unknown cause. Some consider them to be autoimmune diseases. They are often combined under the term inflammatory bowel disease (IBD). This was also the case in the USA survey where 7.3% of IC/BPS patients stated that they suffered from IBD. This is 100x more frequent than in the general population.[23] Further information on Crohn's disease and ulcerative colitis can be found in the chapter on gastrointestinal disorders.

Table 12.4 Examples of associated disorders diagnosed in IC/BPS patients in comparison with the general population [1,24,29]

diagnosis	*prevalence (%)*	
	IC/BPS	*general population*
allergy	40.6	22.5
irritable bowel syndrome	25.4	2.9
sensitive skin	22.6	10.6
vulvodynia	10.9	15.0
fibromyalgia	12.8	3.2
chronic fatigue syndrome	7.7	8.5
migraine	18.8	18.0
asthma	9.2	6.1
Crohn's disease/ulcerative colitis	7.3	0.07
rheumatoid arthritis	4-13	1.0
systemic lupus erythematosus	1.7	0.05
Sjögren's syndrome	8.0	0.5

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic disease characterised by the specific way in which joints are affected by chronic inflammation. The disease is associated with systemic lupus erythematosus and particularly with Sjögren's syndrome. RA occurs in 1-2% of the population. Peeker *et al* mentioned that RA occurred in 13% of their classic IC patients (with "ulcers") and in 4% of IC patients without ulcers.[24] This is about 10x more frequent than in the general population.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the autoimmune disease which has been known for many years to have a relationship with IC/BPS. IC/BPS in SLE patients was often called *lupus cystitis*.

In the USA survey 1.7% of IC/BPS patients stated that they suffered from SLE, this is 34x more frequent than in the general population.

SLE is a generalised autoimmune disease that occurs more frequently in women (10x) and nonwhites

Table 12.5 Summary of the criteria for the diagnosis of systemic lupus erythematosus (American Collega of Rheumatology 1997)

1. malar rash
2. discoid rash
3. photosensitivity
4. oral/nasopharyngeal ulcer
5. arthritis
6. pleuritis or pericarditis
7. proteinuria > 0.5 g/day
8. neurologic/psychiatric disorder
9. haematologic disorder
10. anti-DNA, anti-Sm, or antiphospholipid antibodies
11. antinuclear antibodies (ANA)

(2x). Symptoms and signs that occur most frequently are arthritis, red skin lesions after sun exposure such as a red butterfly lesion of the face, pericarditis and pleuritis (inflamed membranes around the heart and lungs), glomerulonephritis and increased lysis of red blood cells (haemolytic anaemia), white cells (leukopenia) and platelets (thrombocytopenia).

Antinuclear antibodies (ANA) can be found in virtually all untreated patients. In addition, in many SLE patients it is possible to detect one or more other auto-antibodies such as anti-DNA and anti-Sm.

Antiphospholipid antibodies may cause venous and/or arterial thrombosis and a wide variety of complications in pregnancy.

Criteria for the diagnosis of SLE are summarised in Table 12.5. A patient may be said to have SLE if 4 out of 11 items are present at any time.

Sjögren's syndrome

In 1992, as a consequence of the similarity observed between IC/BPS and Sjögren's syndrome, we began a clinical study of IC/BPS patients to investigate whether the presence of a second autoimmune disease could be demonstrated.[27,28] We recently presented data on 100 patients with IC/BPS who were investigated for the presence of Sjögren's syndrome.[29] The IC/BPS patients had characteristic irritative urinary voiding symptoms, no evidence of infection or other bladder disease, typical cystoscopic appearance demonstrable with maximal bladder distension, bladder biopsies ruling out other diseases and showing inflammation in the mucosa and submucosa with lymphocytic infiltrate and increased numbers of mast cells.

Table 12.6 Prevalence of separate items of the American-European criteria for Sjögren's syndrome in 100 patients with IC/BPS

item	*prevalence (%)*
ocular symptoms	68
oral symptoms	60
abnormal ocular test	16
abnormal salivary histology	16
antibodies to SSA/Ro or SSB/La	12

The diagnosis of Sjögren's syndrome was made according to the recent version of the American-European criteria
for Sjögren's syndrome.[30] These consist of six defined items and can be summarized as follows:

1. ocular symptoms
2. oral symptoms
3. ocular signs
4. salivary gland histopathology
5. salivary gland involvement demonstrated by radiology, scan or salivary flow
6. auto-antibodies to SSA/Ro and/or SSB/La

The criteria allow a diagnosis of Sjögren's syndrome if four out of items 1-6 (one of which must be 4 or 6) or three out of items 3-6 are present. This latter situation did not occur in our patient group as we did not further investigate patients for Sjögren's syndrome if both ocular and oral symptoms were absent. Item 3 was only tested if item 1 was present, item 4 was only tested if item 2 was present. Item 5 was never tested because of lack of reproducibility or sensitivity.

Table 12.6 shows the prevalence of each of the investigated items in the IC/BPS patients. Figure 12.2 shows the frequency distribution of the number of items present.

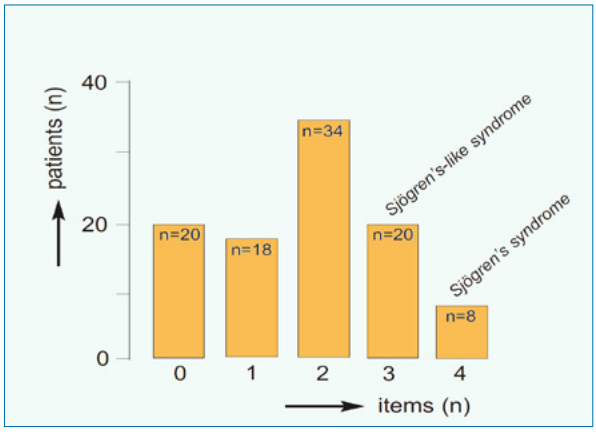

Figure 12.2 *Frequency distribution of the number of items of the European criteria for Sjögren's syndrome present in 100 patients with IC/BPS*

We concluded that in 8% of our patients with IC/BPS a diagnosis of Sjögren's syndrome according to the American-European classification criteria could be made. In addition, 20% of the patients had three items of these criteria and no other disease was found that could account for the present items. In a clinical situation, a diagnosis of Sjögren's syndrome (Sjögren's-like syndrome or incomplete Sjögren's syndrome) is justified in these 20% too.[27,29]

This finding of a relationship between IC/BPS and Sjögren's syndrome has led to a hypothesis in which autoantibodies against the muscarinic M3-receptor, which is present on exocrine cells and the detrusor muscle, play a role in causing early symptoms as well as causing local inflammation later on.[31] Unfortunately, it is not yet possible to reliably demonstrate M3-receptor stimulating and blocking auto-antibodies.

Several authors have also studied the relationship between IC/BPS and Sjögren's syndrome. Peeker *et al* surveyed the clinical records of 222 patients with IC/BPS for diagnoses of autoimmune disorders. 43% of the IC/BPS patients had some type or degree of hypersensitivity/allergy. Rheumatoid arthritis occurred in 10% and inflammatory bowel disease (Crohn's disease and ulcerative colitis) in 1% but no diagnoses of Sjögren's syndrome were found.[24]

Using a questionnaire, Leppilahti *et al*, on the other hand, recently found IC/BPS-like urinary symptoms in 5% of 870 patients with Sjögren's syndrome.[32]

Conclusion

The clinical relevance of the findings is that a high index of suspicion for Sjögren's syndrome is indicated in IC/BPS patients and *vice versa*. The findings also support the possibility of a common pathogenic mechanism such as has recently been proposed.[31]

3. Non-bacterial prostatitis

The prostate is the target of many pathological conditions affecting men of all ages. These conditions range from infections, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) of a still unknown etiology to benign hyperplasia and cancer. CP/CPPS is one of the most prevalent diseases in the urologic clinic and affects men younger than 50 years old. An autoimmune response against prostate antigens has been suggested in patients with CP/CPPS.[46]

The author has seen a high prevalence of nonbacterial prostatitis in male patients with Sjögren's syndrome. This may be less surprising as the lacrimal glands, salivary glands, pancreas and prostate have many properties in common. Definite associations have been found between autoimmune lacrimal gland and salivary gland inflammation (Sjögren's syndrome) and autoimmune pancreatitis (see chapter on liver and pancreatic disorders).

Yasuda *et al* [44] described a case of non-bacterial prostatitis in a patient with Sjögren's syndrome complicated by primary biliary cirrhosis. Histologically, the distribution and subpopulation of infiltrating lymphocytes were similar in the salivary gland, liver, and prostate. Treatment with steroids was successful. Uehara *et al* [45] described six patients with autoimmune pancreatitis with lower urinary tract symptoms and prostate enlargement in four. Their lower urinary tract symptoms (LUTS) improved after steroid therapy.

It is concluded that there is limited and indirect evidence for an association between non-bacterial inflammatory prostate disorders and Sjögren's syndrome. Clinical studies are needed to clarify the association.

4. Vulvodynia (vulvar pain syndrome)

Vulvodynia or *vulvar pain syndrome* is defined as a chronic discomfort in the vulva, often described as a burning pain, without objective findings or specific signs of a neurological disorder. Pain in the urogenital area has major effects on women's daily lives, relationships, sex lives, quality of life and psychological wellbeing.

Vulvodynia is classified according to the localization of the pain in the vulva, whether it is generalized or localized and to whether it arises on provocation of the area or is unprovoked. The pain may also be found in a mixed form.[53]

Several common and many rare disorders may cause vulval burning and/or pain. Common disorders may be due to irritants, allergy or infection.

Irritant dermatitis is common as affected women may have used topical agents on the vulva. Irritants include soap, panty liners, synthetic underwear, moistened wipes, deodorants, douches, lubricants, spermicides, topical medication, urine, faeces, and excessive vaginal discharge.[58] Allergic contact dermatitis may be related to topical medication or sanitary napkins.

Vaginal candidiasis causes vulval burning and itching. Other causes include vulvovaginal atrophy (oestrogen deficiency), recurrent herpes simplex infection, herpes zoster and post-herpetic neuralgia, lichen sclerosus, erosive lichen planus, Behçet's syndrome, cicatricial pemphigoid, Sjögren's syndrome, vulval intraepithelial neoplasia, and carcinoma.[58]

Terminology

The localized, provoked form was previously termed vulvar vestibulitis, as clinical examination of these patients confirmed vestibular erythema and inflammatory cells in skin biopsies from the vestibule. Vestibulodynia, the type of vulvodynia that is localized only in the vestibule, is classified as primary or secondary. Primary vestibulodynia has been present since first tampon use or intercourse. Secondary vestibulodynia develops after a time without pain on intercourse or on insertion of a tampon.

Women who present with a history of pain characterized by a generalized, diffuse distribution arising spontaneously without demonstrable cause were previously given the diagnosis dysesthetic vulvo - dynia. This term has been replaced by generalised, unprovoked vulvodynia.

Epidemiology

The reported prevalence of a disorder strongly depends on the criteria used for the diagnosis and the population studied. Prevalence estimates suggest that women suffering from vulvodynia make up about 4% of the general population,[56] and about 15% of gynecologic clinic populations.[57] A survey of 994 women using stricter criteria suggested that 1.3% of women had ongoing vulvo dynia and 1.7% reported past symptoms.[47]

The cause

The cause of vulvodynia is believed to be a condition with a multifactorial etiology, with organic or functional components. A possible explanation is an increased number of C-afferent nociceptors in the skin.48-50 This suggests a change in the nerve supply to the affected area, which could be a possible pathophysiological basis for increased pain sensitivity on touch or even constant pain. An increase has also been found in the number of mast cells.[51]

A chronic inflammatory process in the mucosa has been suggested to underly the local proliferation of nerves as described above with central pain sensitization as a result.

A correlation between HPV infection and vulvodynia has also been suggested but is not confirmed.

Theories focusing on vulvodynia as a functional disorder are based on the documented effect of treatment by cognitive therapy as well as pelvic floor awareness training and stretching exercises. However, hypertonicity and spasms in the pelvic floor musculature may be secondary to the chronic changes in the mucosa.

The evidence that women with vulvodynia present psychopathological traits to a greater degree than women without vulvodynia seems to be growing. Many diseases, however, with known causes today, were once falsely considered to result from psychopathology. The lesson is that an unknown cause of a disease should not be interpreted as a psychosomatic cause if real evidence is lacking.

Diagnosis

Vulvodynia is a diagnosis that can be made after the exclusion of all known possible causes such as infection (candidiasis, herpes), inflammation (*e.g.* lichen planus), neoplasia (Paget's disease, planocellular carcinoma) or a neurological disorder (herpes neuralgia, spinal nerve compression).

Vulvodynia and associated disorders

Fibromyalgia and irritable bowel syndrome were found to occur 3-4x more often in patients with vulvodynia than in a control group. Vulvodynia patients were also found to have more often a history of chronic yeast vaginitis and urinary tract infections.[55]

Peters *et al* [54] found that almost 60% of women with IC/BPS had vulvodynia.

There are no literature data on the prevalance of vulvodynia in Sjögren's syndrome. However, vulvodynia and Sjögren's syndrome have a common association with fibromyalgia, IC/PBS and irritable bowel syndrome. It is likely, therefore, that vulvodynia occurs more often in patients with Sjögren's syndrome who also have one these associated disorders than in the general population.

Treatment

Many treatment regimes are employed throughout the world in the treatment of vulvodynia. Randomized clinical studies exist and are increasing in numbers on the efficacy of treating vulvodynia with topical applied lidocaine gel, biofeedback, surgery and cognitive behavioral therapy. The evidence behind treatment with antidepressive medicine, local botox injection or local lidocaine injection is based on retrospective cohort studies. It is recommended that the patient initially be encouraged to follow general advice, despite the lack of evidence, on hygiene and then later to try local treatment regimes or systemic treatment regimes.[53] General hygiene advice includes the wearing of cotton underwear, no underwear at night, avoidance of allergenic irritants (*e.g.* perfumes, toiletries, soap) in the vulvar region, application of oil to the vestibule before bathing, application of moisturising cream to the affected area of the vulva after bathing and avoiding the use of panty-liners.[53]

Prognosis

Vulvodynia was traditionally considered a chronic pain disorder, with symptom remission considered rare. Recent surveys of non-clinic-based populations show that in a substantial proportion of women who reported past vulvodynia symptoms the symptoms have resolved. Reed *et al* [52] found that during a 2-year follow-up, each year about one in 50 women developed symptoms of vulvodynia, and one in 10 women with vulvodynia reported remission of symptoms.

5. Dyspareunia

Dyspareunia is defined as painful sexual intercourse and is mainly attributed to pelvic disorders, such as vaginal dryness or vaginal infection. Vaginal lubrication is not related to the production of fluids from the local glands but is mostly a transudate through the vaginal walls and is also derived from the cervical mucous. Insufficient vaginal lubrication has usually multifactorial causes but is most commonly related to an oestrogen deficiency, lack of adequate sexual stimulation or both.

It is well known that dyspareunia is common in patients with Sjögren's syndrome. Skopouli *et al* [59] found that 40% of their premenopausal Sjögren's patients had dyspareunia. An obvious cause was found in half of their patients, although in some patients with normal cytological findings dyspareunia was also reported. Despite the normal vaginal mucosa observed in premenopausal patients with dyspareunia, all patient tissues showed focal perivascular infiltrates in the dermis, a finding which was not seen in the dermis of the normal controls. This lymphocytic perivasculitis could be involved in the pathogenesis of dyspareunia through impaired transudate and inadequate lubrication during sexual intercourse.

Possibly, the vaginal tissues may be affected by an inflammatory process as in other organs, such as the exocrine glands or kidney interstitium.[59]

Dyspareunia in patients with Sjögren's syndrome may also be related to associated disorders such as IC/BPS.[60]

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*
23.01.2009	information on genetics added (ref 43) paragraph added on non-bacterial prostatitis title of chapter changed
10.02.2009	paragraph on vulvodynia and dyspareunia
26.02.2009	minor corrections
16.08.2009	conversion for other DTP program
06.10.2009	many small additions and lay-out changes
15.10.2009	information on history of disease definition (references 61-69); information of potassium sensitivity test (PST) and the antiproliferative factor (APF); ref 70-77. other markers: ref 78-85.
19.10.2009	sequence of paragraphs changed on page 101
26.10.2009	minor changes on pp 99-100; correction ref 41 and addition of PMUI
31.03.2010	inclusion of table 12.3

Pregnancy and lactation 13

A. Pregnancy

Pregnancy in patients with Sjögren's syndrome generally follows a normal course. Pregnancy outcomes are not different in patients with Sjögren's syndrome compared to controls.[10] While some women feel better during pregnancy, others may feel worse and sometimes it makes no difference. The same pattern may be repeated in a subsequent pregnancy, but this is by no means always the case.

There are a number of issues to be considered in relation to pregnancy and Sjögren's syndrome. The first concerns the question as to whether bringing up a child may not be too taxing for the patient. This is a personal decision which needs careful consideration.

The following topics will be discussed in this chapter:

1. the chance that a child will have an autoimmune disease including Sjögren's syndrome during her/his life-time
2. the risk for the child if the mother has auto-antibodies to SSA/Ro or antiphospolipid antibodies
3. the risk for the child if the mother takes drugs during pregnancy and lactation
4. thyroid gland disease and pregnancy

1. The childs' risk for an autoimmune disease

Diseases in first-degree relatives of patients with primary Sjögren's syndrome

Anaya *et al* examined the occurrence of auto immune diseases among first-degree relatives (parents, brothers, sisters, or children) of 101 female patients with primary Sjögren's syndrome (pSS) and of 124 matched controls without autoimmune disease.[3] The mean age at onset was 45 years, the mean duration of the disease 6 years and the mean age of both groups 54 years. One or more autoimmune diseases were found in 6.40% of patients' relatives as compared with 3.85% of controls' relatives (table 13.1). The most frequent auto immune diseases registered among the pSS patients' relatives were autoimmune hypothyroidism, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Five patients' relatives had more than one autoimmune disease (three had 2, one had 3, and one had 4 autoimmune diseases). These results are in line with a previous smaller study.[4]

A sex-specific-relative type occurrence of auto-immune diseases in the pSS families was observed when compared with control families. Nine of 101 pSS patients had a mother affected by at least one autoimmune disease compared with only one father affected. In the control group, there were 6 mothers and 2 fathers affected with one autoimmune disease.

The 3.85% prevalence of autoimmune diseases among first-degree relatives of control individuals is similar to the reported prevalence of such disorders in the general population [5] and in first-degree relatives of controls in other studies of familial autoimmunity. [6,7]

Table 13.1 Total number of autoimmune diseases in first-degree relatives of patients with pSS and of controls [3]

*autoimmune disease **	*first-degree relatives of*	
	patients (n=876)	*controls (n=857)*
pSS	4	0
SLE	8	1
RA	15	10
systemic sclerosis	2	0
PBC	1	0
vitiligo	4	3
MS	1	0
DM type I	3	1
hyperthyroidism	1	1
hypothyroidism	25	17

* pSS: primary Sjögren's syndrome; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PBC: primary biliary cirrhosis; MS: multiple sclerosis; DM: diabetes mellitus

Conclusion
It can be concluded that the risk of a child of a mother with pSS to be diagnosed with an autoimmune disease at a mean age of 54 years is 6.4% (this is 1.66x higher than normal). If an autoimmune disease occurs, the chance that it is autoimmune hypothyroidism is 39%, RA 23%, SLE 12.5% and pSS and vitiligo 2% each. The risk will mainly apply to daughters and rarely to sons.

2. Pathogenic autoantibodies

Antiphospholipid antibodies

Antiphospholipid antibodies are not uncommon in patients with Sjögren's syndrome. These antibodies are sometimes referred to by other names, depending on the method of testing used. They include for example the lupus anticoagulant and anticardiolipin antibodies. In general, they can be the cause of thrombosis (in both veins and arteries, an important difference from other causes of an increased risk of thrombosis), a low platelet count and miscarriages, often - but not always - between 3 and 6 months (figure 13.1).

If one of these problems has occurred and antibodies have been confirmed, the condition is called antiphospholipid syndrome. Treatment consists of anticoagulation. Tablets such as acenocoumarol sometimes in combination with low dose aspirin ("children's aspirin") are used for this anticoagulation treatment. Aspirin alone is insufficient to combat thrombosis.

With antiphospholipid syndrome, anticoagulation is also needed during pregnancy because this increases the chance of a successful pregnancy. Acenocoumarol is contra-indicated during pregnance but low molecular weight heparin can be given, in combination with low dose aspirin (*e.g.* 100 mg/day) if required. Moreover, anticoagulation tablets and standard heparin are not effective for the protection of the pregnancy because they do not cross the placenta.

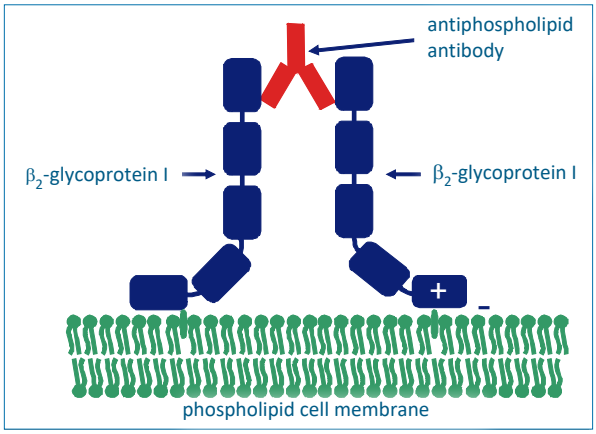

Figure 13.1 *The antiphospholipid antibodies interact with two β2-glycoprotein I molecules. Via mechanisms that are not clarified to date, this binding leads to activation of endothelial cells and platelets and thrombosis.*

There is no consensus on how long patients with thrombosis due to the antiphospholipid syndrome should be treated with anticoagulants. Life-time anticoagulation may be necessary to decrease the risk on life-threatening thromboembolism.

Antibodies to SSA/Ro

Children of women with antibodies to SSA/Ro in their blood run the risk of neonatal lupus (NL) either before or after the birth. These antibodies are mainly found in Sjögren's syndrome, subacute cutaneous lupus erythematosus (SCLE), systemic lupus erythematosus (SLE) and rheumatoid arthritis. SCLE is a relatively benign form of lupus erythematosus occurring in the skin. These antibodies can also be seen in a small percentage of healthy women. Children then also have a risk of developing NL during the pregnancy and after the birth. Conversely, NL only occurs if the mother, and therefore also the child, have antibodies to SSA/Ro.

Clinical features of neonatal lupus

A circular rash on the face is sometimes the only abnormality, but the rash can also occur over the entire body (see figure 13.2). Skin abnormalities usually appear in the first two months of life and particularly following exposure to sunlight. Treatment is not necessary because the rash disappears without scars once the mother's antibodies have disappeared from the child (between 4 and 6 months). The only advice is to avoid exposure to sunlight during this period.

A congenital heart block occurs in 15-30% of the children with NL. More than half of these ultimately need a pacemaker. Other possible clinical features are listed in table 13.2.

Women with antibodies to SSA/Ro have about a 2-10% risk of their child developing NL, of which 20% with a congentital heart block. After one child with NL, subsequent children run a higher risk of developing NL (about 25-30%) or cardiac manifestations of NL (17%).[9,11] The maternal diagnosis was not associated with the outcome in a subsequent pregnancy.[11] The recurrence rate did not correlate with previous use of steroids or the antibody status of the mother. Death of the first child with cardiac NL was not predictive of recurrence of cardiac NL in a subsequent pregnancy. The risk of cardiac NL was similar between male and female children.[11]

Children who have had NL have no increased risk of

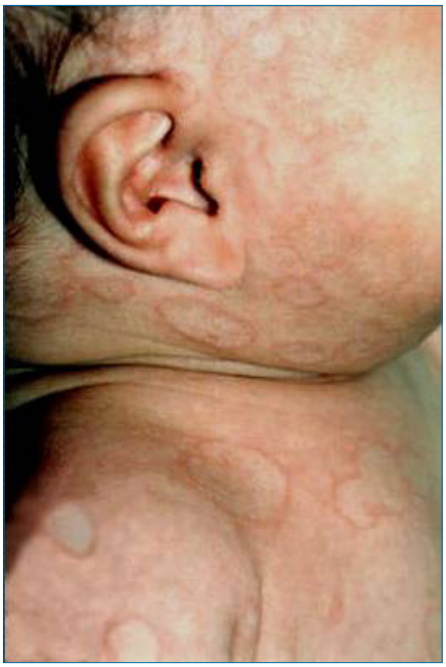

Figure 13.2 *The most common form of skin rash in neonatal lupus*

developing another form of lupus erythematosus later in life. There is, however, a slightly increased risk on other autoimmune diseases. In a study 10 with 49 children with NL and 45 siblings without NL, six children had developed an autoimmune disease at the age of 14 years: juvenile rheumatoid arthritis (n=2), Hashimoto's thyroiditis (n=1), psoriasis and iritis (n=1), diabetes mellitus type I with psoriasis (n=1) and congenital hypothyreoidism and nephrotic syndrome (n=1). All these six children had NL.

Early detection of neonatal lupus

Only women with antibodies to SSA/Ro and/or SSB/La run the risk of having a child with NL. They should be informed that the child may develop a skin rash or blood abnormalities after the birth, but that NL is usually quite harmless unless a heart block develops.

In order to detect any heart block, the foetal heartbeat can be checked between the 15th and 25th week of pregnancy by means of a foetal cardiogram. Advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial first-degree block.[2] If the heartbeat remains normal between the 15th and 25th week of pregnancy, there is no risk of a heart block occurring after birth.

A female patient with antibodies to SSA/Ro and SSB/La has been described where the child developed a heart block in the 19th week of pregnancy. The mother was immediately treated with 4 mg/day dexamethasone, after which the child's heartbeat normalised within six weeks.[1]

Table 13.2 Clinical features of neonatal lupus (these do not all necessarily have to be present)

- skin rash
- low counts of red or white blood cells or platelets
- (mild) hepatitis
- heart block
- other heart defects

Recently, a woman was described with high titer anti-Ro/SSA antibody who presented with fetal AV block (ventricular rate 61 beats per min (bpm)) and right ventricular myocardial echogenicity suggesting fibrosis at 18 weeks' gestation. A 2:1 AV block and intermittent periods of complete independence of atrial and ventricular rate were noted. Dexamethasone 4 mg per os was initiated. Within 1 week fetal heart rate increased to 120-125 bpm with first-degree AV block (PR interval 145 ms) and occasional premature atrial contractions. Sinus rhythm and normal systolic function and ductus venosus Doppler parameters with almost complete resolution of myocardial echogenicity were achieved by the third trimester. At the age of 3 years, the first-degree AV block persisted but cardiac function, growth and development were normal.[8]

Anti-SSA/Ro-associated third-degree congenital heart block is irreversible. Therefore, Friedman *et al* investigated early markers and effective therapy in 98 pregnancies of women with anti-SSA/Ro antibodies.[2] Echocardiograms were performed weekly from 16 to 26 weeks' gestation. PR intervals >150 ms were considered prolonged, consistent with first-degree block. Neonatal lupus developed in 10 cases; 4 were neonatal lupus rash only. Three fetuses had third-degree block; none had a preceding abnormal PR interval, although in 2 fetuses >1 week elapsed between echocardiographic evaluations. Tricuspid regurgitation preceded third-degree block in 1 fetus, and an atrial echodensity preceded block in a second. Two fetuses had PR intervals >150 ms. Both were detected at or before 22 weeks, and each reversed within 1 week with 4 mg dexamethasone. The ECG of 1 additional newborn revealed a prolonged PR interval persistent at

First-degree AV block in neonatal lupus

First-degree AV block in neonatal lupus may be reversible if prompt treatment is given to the mother with 4 mg dexamethasone daily. [1,2,8]

Table 13.3 Classification of a number of a number of drugs according to (certain or probable) risk to the child in pregnancy [9] *See warning on this page.*

probable safe	*risky*	*dangerous*
amitriptyline	chlorpromazine	chlorambucil
amoxicillin	cyclosporine	chloramphenicol
aspirin (applies to low dose only)	diazepam	cocaine
atenolol	haloperidol	cyclophosphamide
azathioprine	methotrexate	ergotamine
captotril	sulfasalazine	methotrexate
chloroquine	5-ASA	metroclopramide
chlorothiazide	temazepam	metronidazole
cimetidine1	tramadol	NSAIDs (all) [b]
colchicine		phenobarbital
co-trimoxazole		
dapsone		
hydroxychloroquine [a]		
nifedipine		
prednisolone		
propranolol		

[a] patients with Sjögren's syndrome are usually advised to stop taking hydrochloroquine, but patients with systemic lupus erythematosus should continue

[b] all prostaglandin synthesis inhibitors such as ibuprofen, naproxen, diclofenac etc. including selective cox-2 inhibitors are dangerous for the fetus as they may induce premature closure of the ductus arteriosus (Botalli's duct)

3 years despite normal intervals throughout gestation. No first-degree block developed after a normal ECG at birth. Heart block occurred in 3 of 16 pregnancies (19%) in mothers with a previous child with congenital heart block and in 3 of 74 pregnancies (4%) in mothers without a previous child with congenital heart block or rash. These data allow the conclusion that first-degree AV block in neonatal lupus may be reversible if prompt treatment is given to the mother with 4 mg dexamethasone daily.

WARNING

The information on the safety of drugs in pregnancy for the developing child is meant as background information.

Do always consult your own physician for all questions on the safety of using drugs during your pregnancy.

3. Medication

Many medicines can better be avoided during pregnancy since it is not known for certain if they are safe for the child (see table 13.3).

Hydroxychloroquine (Plaquenil®) has been found to be safe during pregnancy and lactation but is usually stopped, unless the patient has systemic lupus erythematosus (SLE). Recently, English articles on hydroxychloroquine (HCQ) published between 1982-2007 were systematically reviewed.[12] In pregnant women, it was found that antimalarials, particularly HCQ, decrease lupus activity without harming the baby. It was concluded that HCQ should be given to most patients with SLE during the whole course of the disease, irrespective of its severity, and be continued during pregnancy. Common sense dictates that HCQ, despite it may be less necessary to continue it's use in less severe diseases than SLE (such as Sjögren's syndrome), its use during pregnancy in other diseases is safe too. Prednisolone and low dose aspirin can be taken if required. It is also preferable for pregnant patients to stop taking most other anti-inflammatory drugs and pilocarpine. *Generally speaking, all anti-inflammatory drugs from the prostaglandin synthesis inhibitor group (see chapter 5) should be avoided.* This

Old drugs are safer than new drugs

Drugs that have been on the market for a long time can on average be assumed to be safer than drugs that have been just a short time on the market. It may also be assumed that most side effects are known of drugs that have been on the market for a long time and are frequently used. The list of possible side effects is consequently longer than that for drugs that have been only recently been introduced. A long list of possible side effects does not therefore necessarily mean that the drug is unsafe.

is especially true in the last three months of pregnancy as they can cause premature closure of the ductus arteriosus (Botalli's duct), probably mainly due to the cox-2 inhibiting effect (see chapter 5). The ductus arteriosus is a blood vessel that connects the aorta with the pulmonary artery and bypasses the still undeveloped lungs. Closure normally takes place directly after the birth. Closure before the birth leads to severe strain on the baby's heart because the blood is forced to circulate through the still undeveloped lungs.

4. Thyroid disease and pregnancy

Women on thyroid hormone replacement therapy need a 50% increase of their daily dose during their whole pregnancy to avoid negative effects of (subclinical) hypothyroidism on the developing child.

B. Lactation

Medication

Medication should not be taken when breastfeeding unless essential and proven safe. It is important to prevent the baby from unnecessarily ingesting medication via the breast-milk. Some medicines are safe for adults but harmful to children. Since medicines can occur in breast-milk in high concentrations, the child ingests more than you would initially suspect. If medication is nevertheless necessary, the following points are important:

- use the safest effective medicine;
- take the medication immediately after breastfeeding thebabysoastoensurethelongest possible time before the next feed;
- if possible have the concentration of the medicine in the baby's blood tested.

The use of hydroxychloroquine is considered to be safe during lactation.

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*	*page(s)*
12.01.2009	additional information on the safety of usinghydroxychloroquine during pregnancy and lactation	112,113
26.01.2009	information on follow-up of children who have had neonatal lupus (ref. 10)	118
	paragraph (4) on thyroid replacement therapy during pregnancy.	119
16.08.2009	conversion to another DTP program	
01.10.2009	ref 11 recurrence rate cardiac manifestations of NL	112

Surgery and anaesthesia 14

Surgery and anaesthesia should cause no special problems for people with Sjögren's syndrome, provided that attention is paid to a number of specific points in addition to general aspects.

General evaluation of the risk of surgery

The first step is evaluation of the general risk of surgery, identical to the approach for otherwise healthy people. Based on the principles of evidence-based medicine, the preoperative evaluation 3 of healthy patients should include:

- a screening questionnaire for all patients, see table 14.1; research has shown that no additional benefit is obtained from a complete history, physical examination, or laboratory studies in those patients who answered "no" to all of these questions.[1]
- a history of exercise tolerance for all patients: the ability to walk two blocks on level ground or carry two bags of groceries up one flight of stairs without symptoms are simple questions that can give a rough assessment of patient risk;4 in general, healthy patients who can perform these activities have a low risk for major post-operative complications.
- blood pressure and pulse for all patients
- history and physical examination if one of the above is abnormal, in patients > 60 years, or in those undergoing major surgery
- pregnancy test for women who may be pregnant
- hematocrit for all patients undergoing surgery with expected major blood loss and for patients 65 years or older undergoing major surgery irrespective of potential for perioperative blood loss
- serum creatinine concentration if major surgery, hypotension is expected, nephrotoxic drugs will be used, or the patient is > 50 years
- ECG recommendations as shown in table 14.2, unless obtained within the previous month
- chest x-ray for patients > 50 years undergoing major surgery, or those with suspected cardiac or pulmonary disease, unless done within past six months
- all other tests only if the clinical evaluation suggests a likelihood of disease.

For more detailed professional information and background of evaluation of the general risk of surgery, it is strongly advised to read to the excellent chapter of Smetana in UpToDate.[3]

Table 14.1 Preoperative patient questionnaire [1,3]

1. Do you feel unwell?
2. Have you ever had any serious illnesses in the past?
3. Do you get any more short of breath on exertion than other people of your age?
4. Do you have any coughing?
5. Do you have any wheezing?
6. Do you have any chest pain on exertion (anginal type)?
7. Do you have any ankle swelling?
8. Have you taken any medicine or pills in the last three months (including excess alcohol)?
9. Have you any allergies?
10. Have you had an anesthetic in the last two months?
11. Have you or your relatives had any problems with a previous anesthetic?
12. Observation of serious abnormality from "end of bed" which might affect anesthetic?
13. What is the date of your last menstrual period?

Table 14.2 Guidelines for the use of routine preoperative ECGs [2,3]

- men older than 45 years
- women older than 55 years
- known cardiac disease
- clinical evaluation suggesting the possibility of cardiac disease
- patients at risk for electrolyte abnormalities, such as diuretic use
- systemic disease associated with possible unrecognized heart disease, such as diabetes mellitus or hypertension
- patients undergoing major surgical procedures.

Additional measures for Sjögren's syndrome

Before admission into hospital

If you are taking medication which has an effect on blood clotting, *e.g.* anti-inflammatory agents such as aspirin and other NSAIDs (for example diclofenac, ibuprofen, naproxen), you should normally stop taking these 6 days (aspirin) or 3 days (other NSAIDs) before the operation (see box). For many surgical procedures it is not necessary anymore to stop low dose aspirine, except when there is a high risk of postoperative bleeding (liver and prostate surgery).

If you take corticosteroids on a daily basis, you should continue to take these, including on the day of the operation. Your specialist and the anaesthetist should be informed of this, because when you have a general anaesthetic the dose of corticosteroids needs to be increased during the day of the operation and for a few days afterwards (so-called "stress schedule").

Admission into hospital

It is advisable to take all medication you are currently using with you to the hospital. This particularly applies to artificial tears, artificial saliva and skin creams. In this way you will avoid having to wait a few days until the medication can be supplied by the hospital pharmacy.

The day of the operation

Make sure that you arrange with the anaesthetist to put drops regularly in your eyes throughout the operation so as to prevent damage caused by dryness of your eyes. Also ask the anaesthetist, when preparing you for the operation, not to give you atropine-like drugs intended to make the mucous membranes dryer during the operation. This is not necessary for Sjögren's patients and can cause severe symptoms or disorders after the operation.

If the operation can be done using epidural anaesthesia rather than a general anaesthetic, this would be preferable. However, the anaesthetist usually makes the proviso that a general anaesthetic may still have to be given should it prove necessary during the operation. It is therefore always advisable to discuss the fact that you have Sjögren's syndrome with the anaesthetist.

After the operation

If antibiotics are given in connection with the operation, there will be an increased risk of developing a fungal infection in the mouth. This generally causes a burning mouth with red mucosa and cracks in the corners of the mouth.

Myasthenia gravis

Patients with myasthenia gravis should discuss this health problem with the anaesthetist before the operation because some drugs used in the anaesthetic be harmful to people with myasthenia gravis. See also chapter 15.

Blood clotting and NSAIDs

NSAIDs have an anti-inflammatory effect by inhibiting the enzyme cyclo-oxygenase-2. Older NSAIDs also inhibit cyclo-oxygenase-1 and this is the reason for their damaging effects on the gastric mucosa and the function of platelets (see chapter 5).

The cox-1 effect on platelets is caused by inhibition of tromboxane. This leads to inhibition of thrombocyte aggregation (clumping together of platelets, necessary for blood clotting). Aspirin has the strongest effect of all the NSAIDs on tromboxane because the formation of tromboxane in platelets is irreversibly inhibited. In the case of other NSAIDs, recovery is possible once the NSAID has been stopped.

Platelets normally live for around 7-10 days and are continually replaced. Consequently, recovery of the function of platelets takes longer after the use of aspirin (7 days) than after other NSAIDs (3 days).

It is not necessary to stop taking anti-inflammatory agents that do not inhibit cox-1 before an operation. This applies to hydroxychloroquine, corticosteroids, colchicine and the new selective cox-2 inhibitors (see chapter 5, table 5.1). It may be wise to stop the latter group also because of their intrinsic increased risk on thrombosis.

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date	*addition/modification*	*page(s)*
13.01.2009	information on the evaluation of the general risk of surgery based on the principles of evidence-based medicine	115
17.08.2009	conversion to another DTP program	

Clinical investigations 15

This chapter discusses a number of tests used to aid diagnosis of Sjögren's syndrome, subdivided into eye tests, salivary gland tests and blood tests.

Eye tests

Schirmer test

This test measures the tear production. The folded edge of a strip of filter paper 5x30 mm is placed over the rim of the lower eyelid (figure 15.1) and the eyes are then lightly closed. After 5 minutes, the amount of wetting on the filter paper is measured in mm. This is normally more than 5 mm. The Schirmer test is normal in about 20% of patients with Sjögren's syndrome so a normal test does not exclude the disease. There are two variants: the Schirmer I test and the Schirmer II test. In the Schirmer II test, the measurement is carried out after tear production has been stimulated inside the nose. The Schirmer I test is used in the European criteria (see chapter 4).

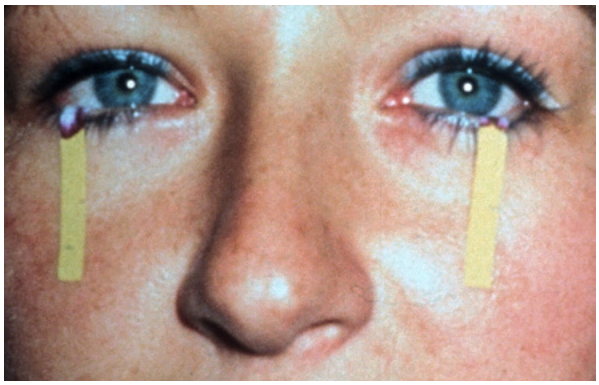

Figure 15.1 *The Schirmer test. The wet part of the strip gets a red colour. Photo: courtesy Dr. O.P. van Bijsterveld.*

Rose bengal dye test

Rose bengal stains cells on the surface of the eye red if they are not fully coated by the mucin layer of tear fluid and/or are damaged (figure 15.2). The result of this test is expressed as the Van Bijsterveld score. A score of 4 or higher (maximum is 9) is abnormal according to the American-European criteria. In patients with Sjögren's syndrome, rose bengal can cause the eyes to sting. The rose bengal test may be painful. Lissamine green is less painful, but is more difficult to evaluate.

Break-up time

The purpose of the break-up time test (BUT) is to measure the quality of the tear fluid. Method: a drop of fluorescein is applied to the eye. After blinking once,

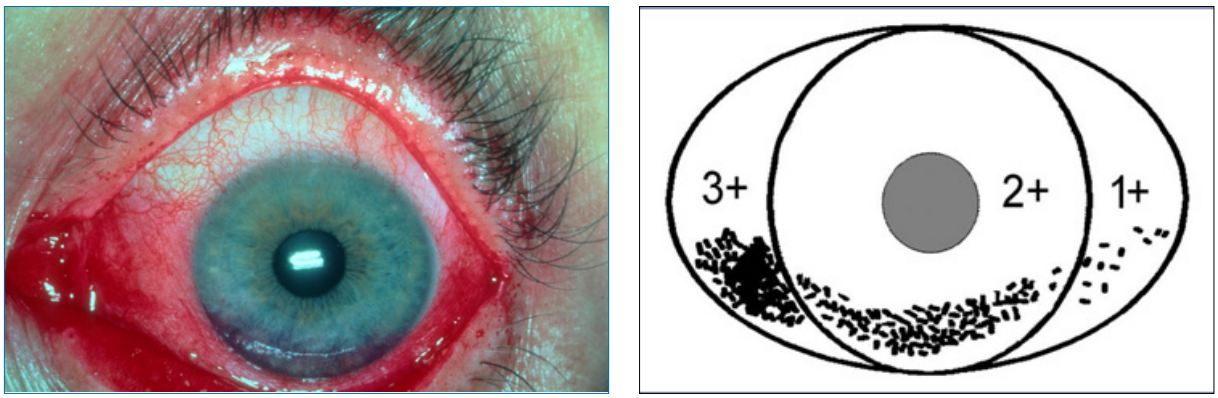

Figure 15.2 *Rose bengal staining. Left: note the red horizontal band across the lower of the eye. Right: the Van Bijsterveld score is determined by adding up the combined score (from 0 to 3; 0 is normal and 3 is the highest level of staining) of the central and two outer sections. The maximum score per eye is therefore 9. In the American-European criteria (see chapter 4), a score of 4 or higher is abnormal. Photo: courtesy Dr. O.P. van Bijsterveld.*

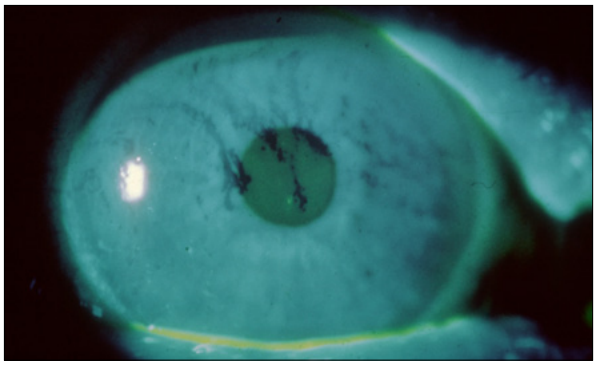

Figure 15.3 *The tear break-up time: the dark spots result from the breaking of the tear film. See text. Photo: courtesy Dr. O.P. van Bijsterveld.*

the patient must keep his eyes open for 10 seconds without blinking. It is then examined how long the tear film remains evenly distributed over the surface of the eye (cornea). After a while, the tear film starts to break up due to surface tension. This can be seen in the form of dark spots in the layer of fluorescein (see figure 15.3). The tear film normally remains intact for 10 seconds or longer. This test is not only abnormal in Sjögren's syndrome but also in blepharitis, a condition causing inflammation of the eyelids due to blockage of the Meibomian gland ducts in the eyelid. Blepharitis can also cause a gritty sensation in the eyes, usually at its worst in the morning (in the case of eye problems caused by decreased tear production or too much evaporation, the symptoms are at their least in the morning and increase during the course of the day).

Salivary gland tests

Lip biopsy

In a lip biopsy, a few tiny salivary glands are removed from the inside of the lower lip under local anaesthetic for examination under the microscope. Since it is important for complete glands to be removed, punch or wedge biopsies are not recommended.

Lip biopsy

- sensitivity for Sjögren's syndrome: 60-82% [4]
- specificity: 85% [2]
- inter-rater reliability by pathologists: poor [3]

see text

Focus score

The biopsy contributes towards the diagnosis of Sjögren's syndrome if the focus score is ≥ 1 (see chapter 4 on diagnostic criteria). The focus score is the number of clusters (foci) of ≥ 50 lymphocytes per 4 mm² of tissue surface (see figure 15.4). Other diseases can also be detected with a lip biopsy, such as sarcoidosis or non-Hodgkin lymphoma.

The lip biopsy is considered to be an important test for the diagnosis of Sjögren's syndrome but abnormal biopsies have been found in 15% of healthy volunteers with focus scores ranging from 2 to 6.

Focus scores did not correlate with age, smoking, serologic findings or salivary flow in these persons.[2] Moreover, 18-40% of Sjögren's patients have a normal lip biopsy.[4] When evaluating the results of the lip biopsy, many sections need to be examined since considerable variation is found. In a recent examination of inter-rater reliability for a group of 5 board-certified pathologists interpreting the same series of labial salivary gland biopsies, the agreement was found to be uniformly poor for judgments of diagnostic status, focus scores, and histological characteristics of biopsy specimens. This lack of reliability is troubling.[3]

Chisholm and Mason grading

In older publications on the evaluation of lip biopsies,

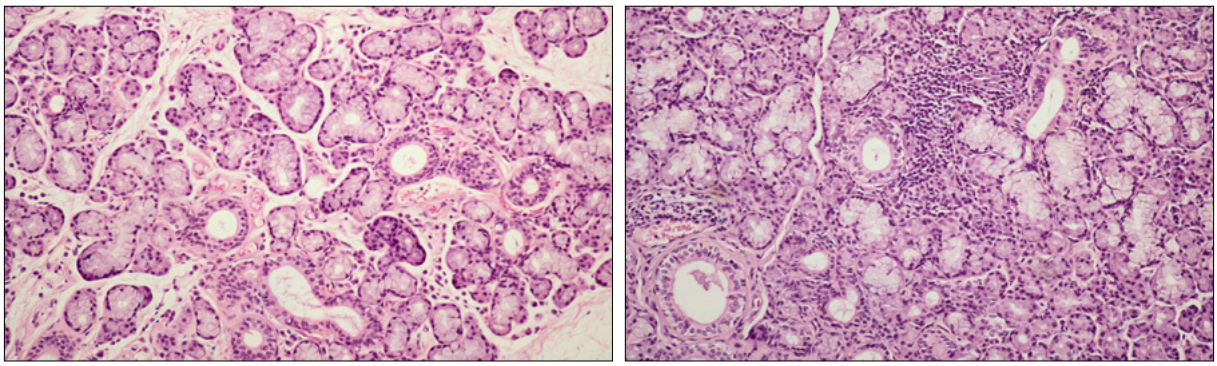

Figure 15.4 *Salivary gland tissue seen under the microscope. Left: normal salivary gland. Right: salivary gland tissue from a patient with Sjögren's syndrome with a focus score greater than 4.*

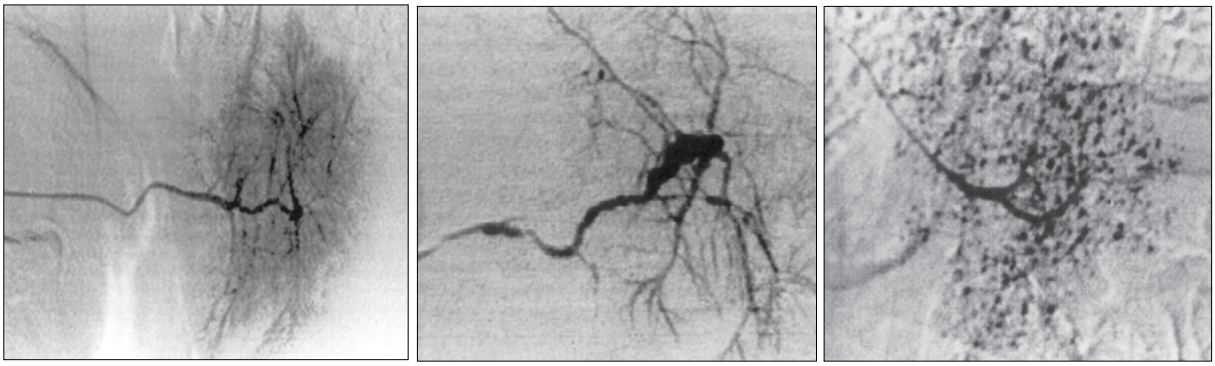

Figure 15.5 *Digital subtraction sialograms of the parotid gland. A: a normal duct system, a homogeneous parenchyma blush and no acinar dilatations. B: wide and destroyed main duct, absent parenchyna blush and no acinar dilatations. C: a sparse overall branching pattern of the ducts, a dilated main duct, an irregular parenchyma blush and many small*

you sometimes come across grade 4 according to Chisholm and Mason. A score of 3 or 4 is equivalent to a focus score of ≥ 1. The meaning of the grades is:

0: absence of infiltrate
1: slight infiltrate
2: moderate infiltrate or < 1 focus
3: 1 focus
4: > 1 focus.

Sialogram

A sialogram is an x-ray of a salivary gland, usually of the parotid gland. A contrast medium is injected into the gland via the duct that opens into the mouth. This medium spreads throughout the duct system, making it visible on an x-ray. In the case of Sjögren's syndrome, there may be dilation or twisting of the ducts and uneven distribution of the contrast medium. A sialogram is therefore only abnormal if the ducts are damaged. Digital subtraction techniques applied to the computer images allow the visual removal of structures other than the duct system. See figure 15.5.

Salivary flow and sialometry

Sialometry is a test to measure salivary flow, the speed at which saliva is produced. This done by asking the patient to chew on a paraffin block for 15 minutes and measurement of the amount of saliva produced in that time. There are several variations on this method.

Sialochemistry

Sialochemistry is the chemical analysis of saliva. It can measure, for example, how much potassium, sodium, protein or amylase is present in the saliva.

Scintigram

A scintigram visualises the uptake and secretion by the salivary glands of a radioactive labelled substance (10 mCi sodium pertechnate ^{99m}Tc) after this substance has been injected into a vein. Rapid uptake and increased concentration in the salivary glands can normally be seen within 10 minutes. After 20-30 minutes, the substance is rapidly secreted into the mouth. In Sjögren's syndrome, lower concentration and less secretion into the mouth are seen.

Blood tests

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate or ESR is used to detect and measure inflammation. The ESR is measured by leaving unclotted blood to stand for an hour in a special test tube. The cells sink to the bottom,

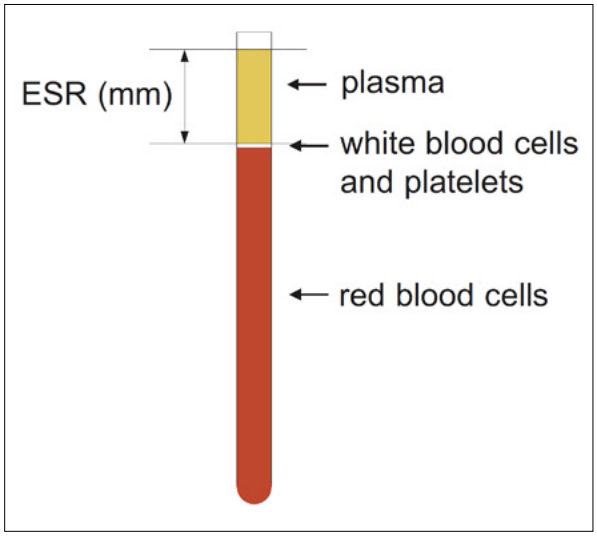

Figure 15.6 *The erythrocyte sedimentation rate (ESR) is the length of the plasma column after the unclotted blood has stood for an hour in a standard test tube.*

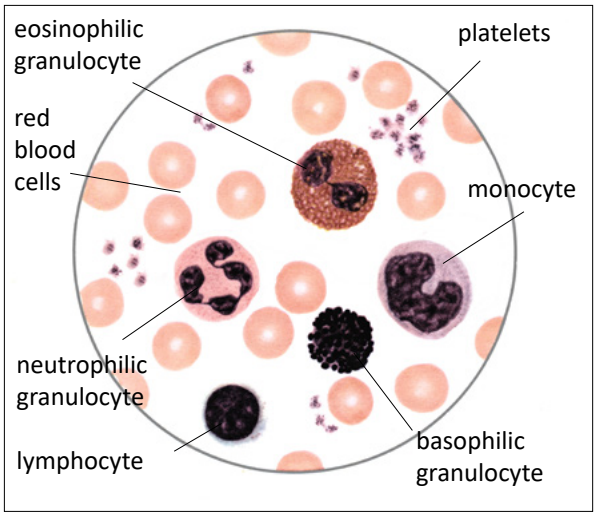

Figure 15.7 *Subdivision of leukocytes in the blood as seen under the microscope. A drop of blood has been smeared over a glass plate and stained with different colours to make the cells visible.*

leaving a column of plasma above them. The ESR is the height of the plasma column in millimetres (figure 15.6). It may be elevated in patients with Sjögren's syndrome, but this is by no means always the case.

An increased ESR does not prove acute inflammation as the ESR is not only influenced by proteins formed by inflammation, but also by antibodies to red blood cells, drugs, anaemia and the concentrations of albumin, IgG and IgM in the blood for example.

CRP

CRP (C-reactive protein) is an acute-phase protein. Acute-phase proteins are found in the blood in increased concentration during episodes of inflammation. The purpose of the test is similar to that of the ESR, but the CRP is more sensitive and not dependent on all kinds of other factors that influence the ESR. An elevated CRP always indicates inflammation.

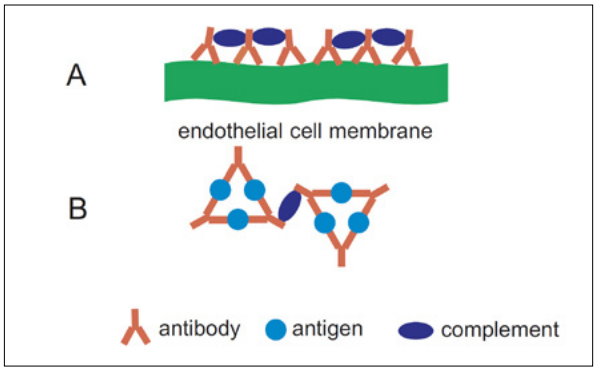

Figure 15.8 *Diagram of immune complexes. A: formation of immune complexes on endothelial cells (the innermost layer of cells inside a blood vessel); B: formation of immune complexes in the bloodstream.*

Leukocytes

Leukocytes are white blood cells. These include neutrophilic, eosinophilic and basophilic granulocytes, lymphocytes and monocytes (see figure 15.7). The number of leukocytes is decreased in a quarter of Sjögren's syndrome patients, usually due to a decreased number of lymphocytes. The decrease is virtually always relatively slight and has no negative effect on resistance to infection. The number of individual white blood cells can also be counted. This is known as leukocyte differentiation.

Hb

The Hb test (haemoglobin concentration) is carried out to detect anaemia. Haemo globin is the red colouring in red blood cells and serves to transport oxygen from the lungs to the body's tissues.

Thrombocytes

The number of thrombocytes (platelets) may be decreased by antibodies to thrombocytes or antiphospholipid antibodies. The decrease is often slight with no consequences for clotting. A decreased thrombocyte count is found in 11% of patients with Sjögren's syndrome.

The number of thrombocytes may also be increased in Sjögren's syndrome as a result of inflammation. This is likewise of no consequence and does not cause increased susceptibility to thrombosis.

Immunoglobulins

Immunoglobulins is the collective name for antibodies. There are five classes as follows: IgG, IgM, IgA, IgE and IgD. IgG is the most important with regard to resistance to infectious diseases. In Sjögren's syndrome, the IgG may be elevated as an indication that the disease is active. The IgA or IgM are also sometimes elevated. Furthermore, monoclonal abnormalities may also be found (see protein screening test). A greatly decreased IgG level is rare in Sjögren's syndrome and causes infection with capsular bacteria such as streptococci or staphylococci.

Complement proteins

Complement proteins play a role in resistance to infection in combination with antibodies. The concentrations of C4 and C3 are sometimes decreased in Sjögren's syndrome. This mainly occurs if they are depleted by the formation of immune complexes (see below) which can lead to inflammation of small blood

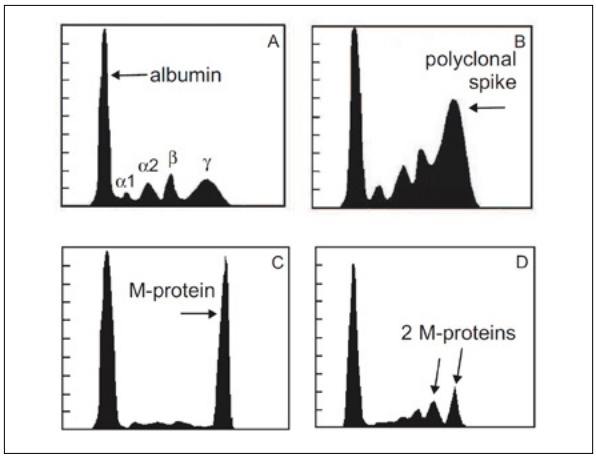

Figure 15.9 Protein screening tests: A. normal; B: poly clonal elevated gamma area; C: monoclonal abnormality; D: oligoclonal (biclonal) abnormality (see text).

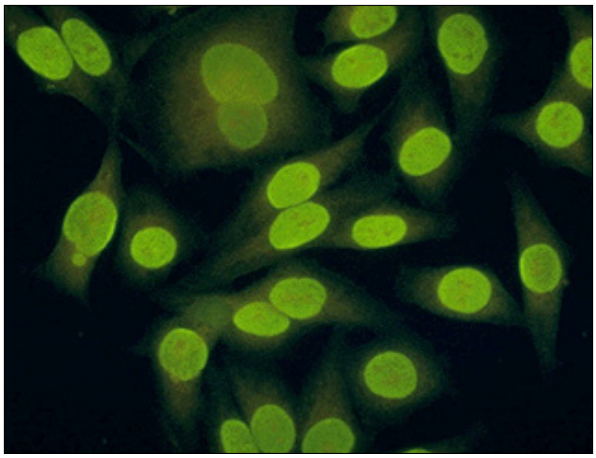

Figure 15.10 *A positive ANA test as seen under the microscope. To carry out the test, use is made of certain cells, e.g. Hep-2 cells, which can bind ANA from the blood sample to be tested. First the test blood is added to the cells and then a marker antibody that emits light under a fluorescence microscope. This marker antibody can only bind to certain parts of the cells via any ANA that might be present in the blood being tested.*

vessels (vasculitis). Elevated counts may be caused by inflammation.

Immune complexes
Immune complexes consist of antibodies, antigens and complement proteins (figure 15.8). They play a role in vasculitis where they are formed on the inside wall of the blood vessels. They often lead to binding and cleavage (depletion) of complement proteins (see above). Immune complexes can be determined in the blood, but for clinical purposes the results are not meaningful.

Cryoglobulins
Cryoglobulins consist of antibodies, antigens and com plement that form a gel at a relatively low temperature, thereby making the blood stickier. Cryoglobulins can cause circulation problems. They occur in malignant blood diseases, auto immune diseases and infections with hepatitis B or C virus. Cryo globulins may cause symptoms resembling Raynaud's phenomenon so patients with Raynaud's phenomenon should be tested for cryoglobulins.

Antibodies in cryoglobulins may be rheumatoid factors (see below) and these can cause symptoms at relatively low concentrations.

Protein electrophoresis
Protein electrophoresis shows the concentration of proteins, particularly albumin and globulins, in the blood or other fluids. Antibodies belong to the (gamma-) globulin group (figure 15.9A). In patients with Sjögren's syndrome, protein screening can show a number of abnormalities such as polyclonal elevation of gammaglobulins (figure 15.9B) or monoclonal and oligoclonal abnormalities (figures 15.9 C and D).

Polyclonal refers to antibodies originating from different plasma cells, while monoclonal refers to identical antibodies (also called M-proteins). Oligoclonal means that there are several monoclonal abnormalities present at the same time. All these abnormalities can occur in Sjögren's syndrome. Testing is important to be able to evaluate the severity of the disease, such as the risk of non-Hodgkin lymphoma.

Amylase
Amylase is an enzyme that plays a role in the digestive process because it breaks down starch. In approximately one third of patients with Sjögren's syndrome, the level of amylase in the blood is moderately elevated due to inflammation in the salivary glands. If there is a very high level of amylase in the blood, it is possible to determine whether it comes from the salivary glands (S-amylase) or from the pancreas (P-amylase).

Glucose
Glucose is sugar in the blood. Elevated levels are an indication of diabetes mellitus. The value of this test in Sjögren's syndrome is to exclude diabetes, particularly if the patient is unable to distinguish properly between dry mouth symptoms and thirst. Whereas Sjögren's patients have a dry mouth but not thirst, in diabetes mellitus this is the opposite.

Autoantibodies in healthy subjects

Many autoantibodies are found in everyone, including the above-mentioned antinuclear antibodies (ANA) and rheumatoid factor. Usually, but not always, the concentrations are lower in healthy people than in people with autoimmune diseases.

The sensitivity of the laboratory tests used to determine the autoantibodies is adjusted to a certain level so as to ensure that the tests are not positive in more than 5% of healthy people.

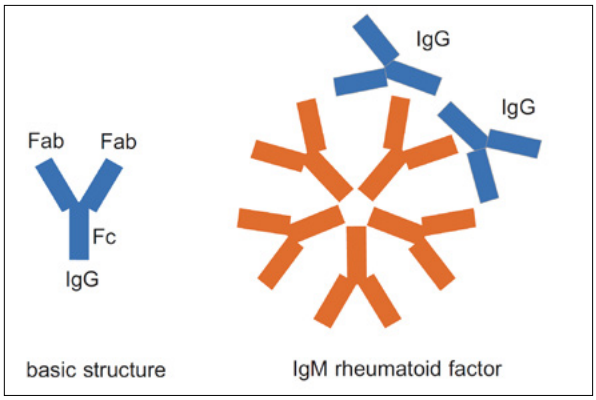

Figure 15.11 *Left: the basic structure of antibodies; Fab is the part of the antibody that the antigen can recognise; IgG consists of one basic unit. Right: IgM consists of 5 basic units; rheumatoid factor is an antibody, usually an IgM, which can bind the Fc element (Fc) of IgG (in this example only two IgG molecules bound by an IgM rheumatoid factor have been illustrated).*

TSH

TSH is an abbreviation for thyroid stimulating hormone. This hormone is produced by the pituitary gland (a small gland under the brain) and stimulates the thyroid into producing thyroid hormone. TSH is elevated in people with an underactive thyroid and is lowered in people with an overactive thyroid. Thyroid diseases often occur during the course of Sjögren's syndrome and are found in approximately 15% of patients.

Lymphocyte subpopulations

Lymphocytes are white blood cells that play a central role in the immune system. With the help of T-lymphocytes, B-lymphocytes can mature into plasma cells that make and secrete antibodies. T-cells are divided into CD4 and CD8 positive T-lymphocytes with different functions.

In Sjögren's syndrome there may be abnormalities in the numbers of lymphocytes in the blood. This may possibly be connected with the distribution of these cells in tissues and blood. The most common differences with healthy people are that relatively more CD5 positive B-lymphocytes occur in the B-lymphocytes and fewer CD8 positive T-lymphocytes.

Sometimes decreased numbers of all T-lymphocytes and B-lymphocytes are found in people suspected of having Sjögren's syndrome. This may be an indication of sarcoidosis rather than Sjögren's syndrome.

Autoantibodies

Antinuclear antibodies

Antinuclear antibodies (ANA, formerly known as ANF or antinuclear factors) is a collective name for anti bodies that are directed against structures within cell nuclei. ANA (figure 15.10) are seen in low percentages in numerous diseases and also in approximately 5% of healthy people. The main reason for determining the presence of ANA is to confirm the diagnosis of systemic lupus erythematosus (SLE) because antinuclear antibodies are almost always present in untreated disease. The ANA test is positive in about 50% of patients with Sjögren's syndrome, but carries no weight in the diagnosis of Sjögren's syndrome.

ANA contain antibodies to SSA/Ro, SSB/La (see below) and to DNA for example. Since these more specific antibodies are determined using different techniques, discrepancies may occur in the test results. For example, in patients with Sjögren's syndrome who have antibodies to SSA/Ro, the ANA test is nevertheless sometimes negative in up to 10%.

Antibodies to SSA/Ro and SSB/La

Antibodies to SSA/Ro and SSB/La are the most characteristic antibodies in Sjögren's syndrome. They can be seen in 60-70% of the patients. SSA/Ro is a complex of three proteins, Ro-52, Ro-60 and calreticulin.

SSA/Ro and SSB/La proteins occur in all body cells of all people and play a role in cell division. It is not clear why patients with Sjögren's syn drome make antibodies to these proteins. There are several methods of testing to determine anti bodies to SSA/Ro and SSB/La.

Tests for antibodies to SSA/Ro and SSB/La are important for the diagnosis of Sjögren's syndrome because they are included in the diagnostic criteria for this disease (see chapter 4). As some patients only have 52 kD SSA/Ro antibodies, tests should be able to detect both 52 and 60 kD antigens. Antibodies to SSA/Ro also occur in patients with subacute cutaneous lupus erythematosus, systemic lupus erythematosus, neonatal lupus and dermatomyositis (anti-SSA/Ro 52 in particular).

Antibodies to SSA/Ro and/or SSB/La can make people more sensitive to sunburn and may cause neonatal lupus in newborn babies (see chapter 12).

Rheumatoid factor

Rheumatoid factor is an antibody, usually of the IgM class, that is directed to the Fc component of IgG (figure 15.11). Rheumatoid factor can be seen in 5% of healthy people, in about 70% of patients with rheumatoid arthritis and in about 40% of patients with Sjögren's syndrome. Determination of rheumatoid factor is only meaningful if rheumatoid arthritis is suspected, but the presence of rheumatoid factors is not sufficient to make this diagnosis.

Anti-CCP

Antibodies to CCP (cyclic citrullinated peptide, citrulline is an amino acid, amino acids are the building blocks of proteins) occur in approximately half the patients with rheumatoid arthritis and rarely in people with other diseases. It is a new test, developed in Nijmegen in the Netherlands, which may possibly replace rheumatoid factor tests in the future. This test is slightly less sensitive in rheumatoid arthritis, but far more specific than determination of the rheumatoid factor. The anti-CCP test is virtually always negative in Sjögren's patients with a positive rheumatoid factor but without rheumatoid arthritis.[1]

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Side effects of drugs in Sjögren's syndrome

16

Drugs play an important role in the treatment of diseases, but every drug has its advantages and disadvantages.

Use of a drug is only justified if the expected advantages are greater than the disadvantages. In order to be able to evaluate the advantage, it needs to be clear what the purpose of the treatment is and how the effect can be evaluated after a specific period of time.

The disadvantages of drugs may subdivided into different categories including allergic reactions, general side effects, disease-dependent side effects and interactions with other drugs. Special situations may also arise if the kidney function and/or liver function are impaired.

Dryness

In the case of patients with Sjögren's syndrome, it is important to note that a possible side effect of many drugs is dryness of the mucous membranes. This is sometimes scarcely noticeable, but in Sjögren's patients the existing complaints of dryness may be greatly exacerbated as a result of using the drug. It is often possible to replace a drug with this side effect by another drug which does not have this side effect.

It is impossible to give a comprehensive summary here of the drugs that can cause dryness of the mucous membranes. Package inserts usually provide detailed information about this. Table 16.1 gives examples of the generic names (*i.e.* not the brand names) of a number of these drugs.

Constipation

A large number of drugs can cause constipation. These include all diuretics and prostaglandin synthetase inhibitors (these include most anti-inflammatories, with the exception of *e.g.* hydroxychloroquine, colchicine, dapsone and corticosteroids).

Pregnancy

A special warning applies to the use of drugs during pregnancy. A number of specific drugs are known to have a potential risk of causing deformities in the foetus developing in the uterus and should therefore absolutely not be taken during pregnancy. In addition, many drugs are also secreted in breast milk. Since the effect of most drugs in pregnancy is as yet unknown, these too should be avoided as far as possible. See also chapter 11.

Sjögren's syndrome and myasthenia gravis

A small percentage of patients with Sjögren's syndrome

Table 16.1 Examples of drugs which can cause or exacerbate dryness of mucous membranes

anti-diarrhoea drugs
loperamide

antihistamines
loratadine
promethazine
hydroxyzine
terfenadine
cetirizine

anti-inflammatories
piroxicam
ibuprofen
ketoprofen
naproxen

analgesics
morphine

antiasthmatics
salbutamol
ipratropium

betablockers
metoprolol
pindolol
atenolol

calcium channel blockers
nicardipine

sleeping tablets
triazolam
flurazepam
temazepam

tranquillizers
hydroxyzine
lorazepam
meprobamate
oxazepam
diazepam
alprazolam

anticonvulsants
carbamazepine

antidepressants
clomipramine
amitriptyline
imipramine
desipramine

antihypertensives
methyldopa
captotril, lisinopril
clonidine
guanethidine
reserpine

diuretics
spironolactone
chlorthiazide
triamterene
chlorthalidone
furosemide

antispasmodics
hyoscyamine
atropine
oxybutynin
propantheline
scopolamine

Table 16.2 Drugs which can exacerbate myasthenia gravis or trigger symptoms in subclinical myasthenia gravis

antibiotics
aminoglycosides
tobramycin
gentamycin
neomycin
kanamycin
ciprofloxacin
norfloxacin
tetracyclines
sulphonamides
penicillins
azithromycin

quinolones
quinine
quinidine
chloroquines

various
magnesium preparations
anaesthetic agents

Table 16.3 Drugs which could form a risk with myasthenia gravis

betablockers
propranonol
oxprenolol
timolol
atenolol
labetolol
metoprolol

psychotropics
lithium carbonate
phenothiazines
amitriptyline
imipramine
amphetamines
haloperidol

calcium channel blockers
verapamil

anticonvulsants
phenytoin
barbiturates
ethosuximide
carbamazepine
gabapentin

drugs for eye disorders
timolol
betaxolol
ecothiophate

various
procainamide
riluzole
drugs used for anaesthesia

also have myasthenia gravis (see chapters 2 and 7). It is also possible to have a mild form of myasthenia gravis (MG) which under normal circumstances produces no symptoms (subclinical MG).

Certain drugs can exacerbate existing MG and have a triggering effect in the case of subclinical MG. In both forms of MG, problems may occur with drugs used for anaesthesia. This means that if a Sjögren's patient knows that (s)he also has MG, this should always be discussed with the anaesthetist before an operation.

If a patient has a problem with double vision, drooping eyelids or muscular weakness due to the use of certain drugs, this could be a subclinical form of MG.

Double vision and muscular weakness as a side effect of drugs

Everyone, but especially patients with auto-immune diseases such as Sjögren's syndrome, who gets double vision and/or (exacerbation of) muscular weakness as a side effect of a drug may possibly have a mild form of myasthenia gravis. These side effects should be reported to your specialist.

This should be discussed with the patient's specialist so that tests can be carried out to find out if this is indeed the case. Please note that both hydroxychloroquine (Plaquenil®) and chloroquine (Nivaquine®) belong to the chloroquine group in this list.

Table 16.2 lists a number of drugs known to sometimes exacerbate an existing MG or trigger symptoms in the case of subclinical MG.

Table 16.3 lists a number of drugs which could form a risk to patients with MG for the same reason.

Patients with Lambert-Eaton Myasthenia Syndrome (LEMS) run the same risk (see also chapter on disorders of the nervous system).

Sjögren's syndrome and hypertension

Hypertension is a common disease with major risks for stroke and myocardial infarction. Pharmacological treatment of hypertension is aimed at reducing these risks by lowering the blood pressure. Several groups of drugs are used with different effects, side-effects and costs. Relatively old are the thiazide-type diuretics and *β*-receptor blockers. Newer antihypertensive agents are calcium-channel blockers, ACE inhibitors, angiotensin-II receptor antagonists and renin inhibitors.

Diuretics and to a lesser degree, betablockers may increase the dryness of eyes and mouth.

Calcium channel blockers may improve symptoms of Raynaud phenomenon whereas betablockers are contraindicated in Raynaud phenomenon.

Pharmacological treatment of hypertension

Diuretics and blockers have been used widely in the treatment of hypertension and were recommended as

Betablockers for hypertension

Betablockers should not remain first choice in the treatment of primary hypertension.

Lindholm LH et al 2005 [1]
National Collaborating Centre for Chronic Condition 2006 [2]

IMPORTANT

The comments on betablockers in this chapter, only apply if they are prescribed for hypertension and NOT IF PRESCRIBED FOR CARDIOLOGICAL INDICATIONS.

first-line drugs in hypertension guidelines.

Lindholm *et al* searched The Cochrane Library and PubMed for betablocker treatment in patients with primary hypertension.[1] Thirteen randomised controlled trials (n=105951) were included in a meta-analysis comparing treatment with betablockers with other antihypertensive drugs. Seven studies (n=27433) were included in a comparison of betablockers and placebo or no treatment.

The relative risk of stroke was 16% higher for betablockers than for other drugs. There was no difference for myocardial infarction. When the effect of betablockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all betablockers, about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

Lindholm *et al* conclude that in comparison with other antihypertensive drugs, the effect of betablockers is less than optimum, with a raised risk of stroke.[1] Hence, they believe that blockers should not remain first choice in the treatment of primary hypertension.

For the general population, the following recommendations [2] have been given by the National Collaborating Centre for Chronic Conditions:

1. In hypertensive patients aged 55 or over, or black [a] patients of any age, the first choice for initial therapy should be either a calcium channel blocker or a thiazide-type diuretic.

2. In hypertensive patients younger than 55, the first choice for initial therapy should be an ACE inhibitor.[b]

3. If initial therapy was with a calcium channel blocker or a thiazide-type diuretic and a second drug is required, add an ACE inhibitor.[b]
   If initial therapy was with an ACE inhibitor, add a calcium-channel blocker or a thiazide-type diuretic.

[a] including both Black African and Black Caribbean patients, not Asian, Chinese, mixed-race, or other ethnic groups

[b] or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated

Diuretics may increase complaints of dryness in patients with Sjögren's syndrome and should therefore not be a first choice in the treatment of hypertension in Sjögren's syndrome.

The recommendations above can thus be modified for Sjögren's patients as follows:

1. In hypertensive Sjögren's patients aged 55 or over, or black [a] patients of any age, the first choice for initial therapy should be a calcium channel blocker.

2. In hypertensive Sjögren's patients younger than 55, the first choice for initial therapy should be an ACE inhibitor.[b]

3. If initial therapy was with a calcium channel blocker and a second drug is required, add an ACE inhibitor.[b]
   If initial therapy was with an ACE inhibitor, add a calcium channel blocker.

References

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Recommendations for treatment of hypertension patients with Sjögren's syndrome *(see text)*

1. In hypertensive Sjögren's patients aged 55 or over, or black patients of any age, the first choice for initial therapy should be a calcium channel blocker.

2. In hypertensive Sjögren's patients younger than 55, the first choice for initial therapy should be an ACE inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated).

3. If initial therapy was with a calcium channel blocker and a second drug is required, add an ACE inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated).
   If initial therapy was with an ACE inhibitor, add a calcium channel blocker.

Disease activity, disease damage and symptom scores 17

Introduction
It is widely accepted that to capture the totality of the effect of a disease on a patient, three aspects of the disease must be assessed: [8,9]

a. *disease activity*, which is potentially reversible with treatment

b. *disease damage*, which is irreversible, and can remain the same or increase in time

c. the patient's perception of the *symptoms* of the disease

The assessment of both disease activity and disease damage is therefore fundamental for the care of patients with chronic diseases to optimize therapy and the long-term prognosis.

Symptom scores
Symptom scores may yield different outcomes depending on whether they are used by the physician or by the patient.[10] In general, symptom scores from patients depend at least on:

a. activity of the disease

b. damage caused by the disease

c. psychological coping capacity of the patient

d. the patient's ability to translate the perception of the severity of the symptoms into an answer to the question of the scoring system

Scores for symptoms, whether as perceived by doctors or by patients, overlap not only with *quality of life* scores but also with scores for disease activity and damage. This property has made them popular as outcome measures despite or just because of the fact that they measure a complex mixture of various aspects of diseases and the patient's or doctor's perception.

There is no evidence to date that improvement on symptoms scores also improves disease activity or prevents damage by the disease. Symptom scores are therefore only optimal primary outcome parameters for purely symptomatic treatment trials, and as long as they are designed from the patient's perspective.

> ***Disease damage is irreversible***
>
> Disease-modifying drugs prevent damage via effects on various pathogenic mechanisms of active clinical and/or subclinical disease. However, drug intervention cannot improve existing damage as this is irreversible. If a new drug were able to heal a previously irreversible lesion, this type of damage should not be classified as disease damage anymore but as disease activity.
>
> The *difference*, therefore, between disease activity and disease damage is based on the efficacy of present treatments.

Definition of disease activity and disease damage
The course of many chronic diseases, including Sjögren's syndrome, is characterized by periods of disease activity (flares) and disease inactivity. Flares show variable resolutions or may persist. It is important to distinguish disease activity from damage as activity may be reversible while damage is permanent (irreversible). Relevant outcome scores in clinical studies are therefore a decrease in disease activity, prevention of additional damage, and improvement in symptoms and quality of life as perceived by the patient (figure 17.1).

Disease activity may be defined as actual changes in anatomy, physiology, or function causing symptoms and/or future damage that are reversible with treatment.[8] Activity scores may measure separate disease manifestations such as pain and fatigue (see chapter on fatigue) or measure all possible features that can be attributed to disease activity as a single score.

Disease damage may be defined as irreversible

changes in anatomy, physiology, or function accumulated since the onset of the disease, from the disease itself, comorbid conditions or as a result of therapy.[8]

In these definitions, disease damage that has been effectively treated by removal (*e.g.* resection of a parotid gland) should still count as damage. If a new drug were able to heal a previously irreversible lesion, this type of damage should not be classified as disease damage anymore but as disease activity.

Damage is usually considered to be the result of active disease and the absence of active disease is usually considered not to cause organ damage. However, organ damage may occur even when the disease is clinically inactive and without symptoms. This was clearly shown in patients with inactive rheumatoid arthritis in whom subclinical arthritis was detected by imaging techniques explaining their structural deterioration despite the clinical remission.[11] This kind of silent tissue damage occurs in many other chronic diseases such as in sarcoidosis (interstitial pneumonia with lung fibrosis), systemic lupus erythematosus with antiphospholipid syndrome (premature cardiovascular disease), cardiomyopathies, atherosclerosis, various malignancies, Sjögren's syndrome (*e.g.* sensory polyneuropathy) and many others.

A lot of work has been done to develop a damage scoring system for diseases characterized by systemic vasculitis such as Wegener's granulomatosis. These diseases are characterized by severe disease activity and severe disease damage that are affected in a completely different way by various drugs. Consequently, these diseases are usually treated with combinations of drugs. The Vasculitis Damage Index (VDI) deals with features which have occurred since the onset of vasculitis regardless of whether they are attributable to vasculitis or not.[12] Examples of other chronic diseases for which separate scoring systems are used for disease activity and disease damage are rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, chronic liver disease, systemic sclerosis and Crohn's disease.[13-21]

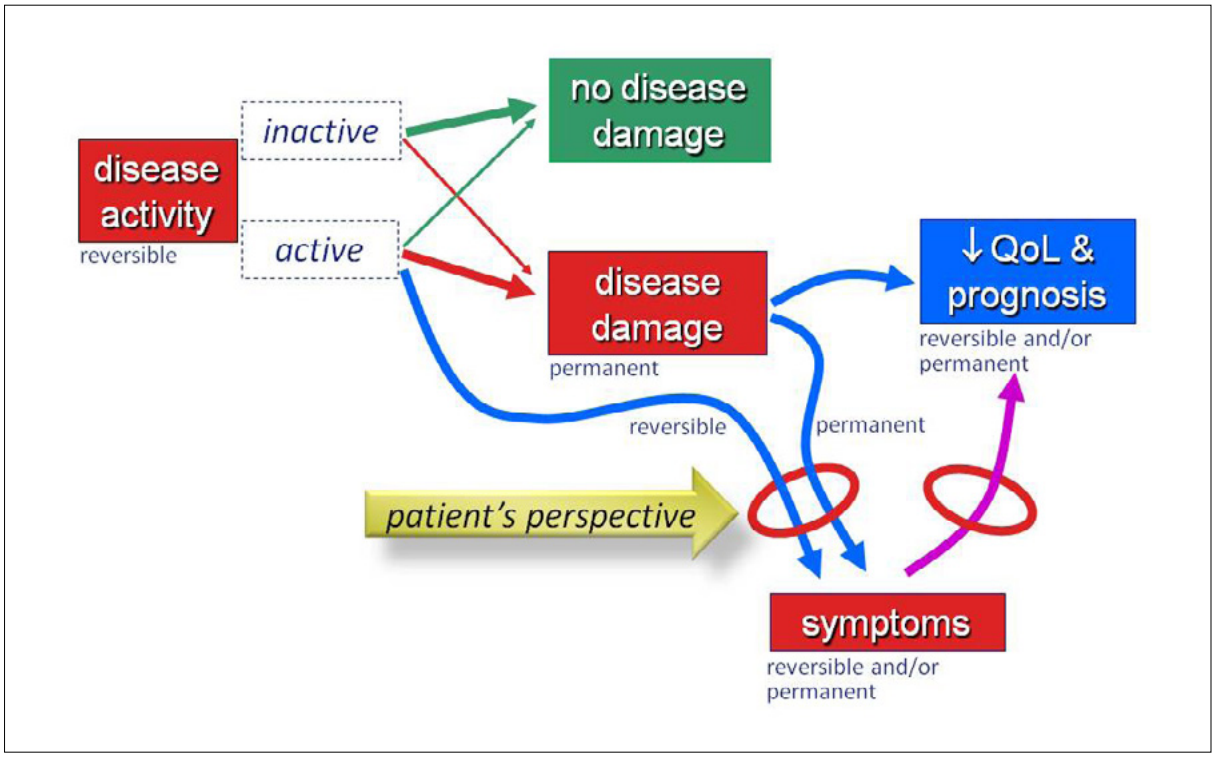

Figure 17.1 Schematic representation of the relationship between disease activity, disease damage, symptoms and prognosis including quality of life (QoL). Symptoms result from a complex interaction between active disease, disease damage and patient properties. Symptom scores are therefore only optimal primary outcome parameters for purely symptomatic treatment trials.

DISEASE ACTIVITY

Two research groups have developed measurements for disease activity and disease damage: the group of Bowman in the UK and the group of Vitali in Italy (table 17.1). The approach of both groups was more or less similar. In general, the selection of collected data by Bowman's group seems to be based on a broader and more international consensus. Vitali's scales seem more simple and easier to use as compared to the very extensive scores proposed by the British group. The results of both groups are mainly based on expert opinions and so-called training samples. Vitali's and Bowman's disease activity scores are given in an appendix to this chapter (tables 17.7 and 17.8). They are likely to be replaced now by the new ESSDAI scoring system.

Table 17.1 Disease activity and damage scores

first author, year	*measurement*	*patients (n)*
Bowman 2004 [1]	fatigue, discomfort	104
Bowman 2007 [3]	disease activity	104
Vitali 2007 [5]	disease activity	206
Vitali 2007 [5]	disease damage	206
Barry 2008 [4]	disease damage	104

ESSDAI

Recently, the EULAR (European League Against Rheumatism) published the ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index).[7] The ESSDAI is a consensus systemic disease activity index developed by 39 Sjögren's syndrome experts, including Bowman and Vitali, who participated in an international collaboration.

Twelve organ-specific so-called domains contributing to disease activity were identified (see table 17.2). For each domain, features of disease activity were classified in 3 or 4 levels according to their severity. Data from 96 patients with systemic complications of primary Sjögren's syndrome were used to generate 702 realistic vignettes for which all possible systemic complications were represented. Using the 0-10 physician global assessment (PhGA) scale, each expert scored the disease activity of 5 patient profiles and 20 realistic vignettes. Multiple regression modelling, with PhGA used as the dependent variable, was used to estimate the *weight* of each domain. The domains were, with the weight and maximal activity level within parentheses: constitutional (3; 2), lymphadenopathy (4; 3), glandular (2; 2), articular (2; 3), cutaneous (3; 3), pulmonary (5; 3), renal (5; 3), muscular (6; 3), peripheral nervous system (5; 3), central nervous system (5; 3), hematological (2; 3) and biological (1; 2).

All 12 domains were significantly associated with disease activity in the multivariate model, domain weights ranged from 1 to 6. The ESSDAI scores varied from 2 to 47 and were significantly correlated with PhGA for both real patient profiles and realistic vignettes.

The authors appreciated that a systemic index needs to distinguish between disease activity (*reversible*) and disease damage (*irreversible*). The most frequent approach to avoid scoring disease damage as disease activity, is to consider manifestations as active only if "new" or "worsening." Under these scoring systems, when patients are evaluated at two time points, a persistent manifestation will not be rated at the second time point, which may cause an erroneous interpretation of improvement even though the patient's condition has not changed. To avoid this, all ESSDAI items were defined without reference to a previous assessment, but with an advice not to rate as active stable long-lasting features related to damage.

Conclusion

The ESSDAI is a clinical index designed to measure disease activity in patients with primary Sjögren's syndrome. Further studies are needed to assess the reliability and sensitivity to change of the ESSDAI. Once validated, if uniformly applied, the ESSDAI might enable comparison between studies and facilitate clinical research into primary Sjögren's syndrome.

2. PATIENT REPORTED SYMPTOMS INDEX

According to the authors of the ESSDAI paper, a second index currently in development by EULAR is a patient-administered questionnaire to assess patient symptoms, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI).[7] The authors conclude that after its development, the use of both the ESSDAI and ESSPRI for outcome assessment in randomized controlled trials should allow for assessing all facets of the disease.

This conclusion, however, does not address the fact that disease damage may occur without apparent disease activity, and that disease activity may or may not result in disease damage. Therefore, separate scores for disease damage are necessary as well.

Table 17.2 The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Domain and item definitions and weights

Domain [Weight]	*Activity level*	*Description*
Constitutional [3] *Exclusion of fever of infectious origin and voluntary weight loss*	No=0 Low=1 Moderate=2	Absence of the following symptoms Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5 to 10% of body weight Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] *Exclusion of infection*	No=0 Low=1 Moderate=2 High=3	Absence of the following features Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or spleno-megaly (clinically palpable or assessed by imaging) Current malignant B-cell proliferative disorder
Glandular [2] *Exclusion of stone or infection*	No=0 Low=1 Moderate=2	Absence of glandular swelling Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular [2] *Exclusion of osteoarthritis*	No=0 Low=1 Moderate=2 High=3	Absence of currently active articular involvement Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) 1 to 5 (of 28 total count) synovitis ≥ 6 (of 28 total count) synovitis
Cutaneous [3] *Rate as "No activity" stable long-lasting features related to damage*	No=0 Low=1 Moderate=2 High=3	Absence of currently active cutaneous involvement Erythema multiforma Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary [5] *Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)*	No=0 Low=1 Moderate=2 High=3	Absence of currently active pulmonary involvement Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test. Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO}≥ 40% or 80%>FVC≥60% Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO}< 40% or FVC< 60%
Renal [5] *Rate as "No activity" stable long-lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first*	No=0 Low=1 Moderate=2 High=3	Absence of currently active renal involvement with proteinuria< 0.5 g/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥60 ml/min) Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/d and without hematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/d or hematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement

Table 17.2 (*continued)* The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Domain and item definitions and weights

Domain [Weight]	*Activity level*	*Description*
Muscular [6] *Exclusion of weakness due to corticosteroids*	No=0 Low=1 Moderate=2 High=3	Absence of currently active muscular involvement Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N <CK ≤ 2N) Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK ≤4N), Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (>4N)
PNS [5] *Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease*	No=0 Low=1 Moderate=2 High=3	Absence of currently active PNS involvement Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia) Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS [5] *Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease*	No=0 Low=1 High=3	Absence of currently active CNS involvement Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.
Hematological [2] *For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No=0 Low=1 Moderate=2 High=3	Absence of auto-immune cytopenia Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm3), and/or anemia (10 < hemoglobin < 12 g/dl), and /or thrombocytopenia (100,000 < platelets < 150,000/mm3) Or lymphopenia (500 < lymphocytes < 1000/mm3) Cytopenia of auto-immune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm3), and/or anemia (8 ≤ hemoglobin ≤ 10 g/dl), and/or thrombocytopenia (50,000 ≤ platelets ≤ 100,000/mm3) Or lymphopenia (≤500/mm3) Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm3), and/or or anemia (hemoglobin < 8 g/dl) and/or thrombocytopenia (platelets <50,000/mm3)
Biological [1]	No=0 Low=1 Moderate=2	Absence of any of the following biological feature Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

CIDP= chronic inflammatory demyelinating polyneuropathy; CK= creatine kinase; CNS= central nervous system; DLCO= diffusing CO capacity; EMG= electromyogram; FVC= forced vital capacity; GFR= glomerular filtration rate; Hb= hemoglobin; HRCT= high-resolution computed tomography; IgG= immunoglobulin G; NCS= nerve conduction studies; NHYA= New York heart association classification; Plt= platelet; PNS=peripheral nervous system;

Calculation of the ESSDAI score

The ESSDAI score is obtained by addition ot the twelve domain scores.[7] Each domain score is obtained by multiplying the activity level with the domain weight. The maximum theoretical ESSDAI score is 123. The highest score in the ESSDAI study was 47.

3. DISEASE DAMAGE

Damage to organs is irreversible by definition and, as outlined before, should be distinguished from disease activity. As far as functions of the lacrimal and salivary glands are concerned, it has become likely from the efficacy of pilocarpine in 50-60% of patients with Sjögren's syndrome, that diminished Schirmer and salivary flow tests do not always reflect damage but more often diminished function due to blocking autoantibodies to the muscarinic M3 receptor (see chapter 3). The presence of these tests in damage scores, therefore, may be questioned.

The recently developed ESSDAI[7] activity score does not contain measurements of disease damage. Therefore, the indices as developed in addition to the activity scores previously by Vitali and Bowman, are discussed here as well. These are the 1. Sjögren's Syndrome Disease Activity Index and the 2. Sjögren's Clinical Activity Index, respectively.

1. Sjögren's Syndrome Disease Damage Index
Vitali's Sjögren's Syndrome Disease Damage Index (SS-DDI) consists of damage scores to six organ groups, see table 17.3.[2] Note that the cut-off point of the Schirmer test, probably by mistake or typing error, differs from that of the American-European criteria (< 5 mm *versus* 5 mm).

Table 17.3 SSDDI: items of the Sjögren's Syndrome Disease Damage Index (Vitali *et al* [2])

	score
oral/salivary damage	
- salivary flow <1.5 ml/15 min	1
- loss of teeth	1
ocular damage	
- Schirmer-I test <5 mm in 5 min*	1
- corneal ulcers, cataracts, chronic blepharitis	1
neurologic damage	
- central nervous system involvement	2
- peripheral neuropathy	1
pleuropulmonary damage	2
- pleural fribrosis or interstitial fibrosis or functional damage	
renal impairment	2
- any of: increased serum creatinine, reduced glomerular filtration rate, tubular acidosis, nephrocalcinosis	
lymphoproliferative disease	5
- any of: B cell lymphoma, multiple myeloma, Waldenström's macroglobulinemia	

* should be ≤ 5 mm according to the American-European criteria

2. Sjögren's Syndrome Damage Index

Barry *et al* developed the Sjögren's Syndrome Damage Index based on previous proposals[1,6] and a lengthy process of refinement involving both appraisal by specialists in the fields of ophthal mology, oral medicine and rheumatology, and a comprehensive statistical validation.[4]

The index provides a three-domain assessment of patients: ocular, oral and systemic damage (tables 17.4-17.6). A score of 1 is allocated to each item and no weighting of scores is applied. Interestingly, the three domains showed only week correlations and, therefore, the authors suggest to consider them as three separate rating scales. They accept, however, that there may be situations in where a "total damage" score may be useful, albeit interpreted with caution.

Table 17.4 Sjögren's Syndrome Damage Index (Barry *et al* [4]): ocular damage

- corneal scarring
- Schirmer-I result 0 mm/5 min in both eyes
- tear duct surgery (punctal plugs or cautery)

Table 17.5 Sjögren's Syndrome Damage Index (Barry *et al* [4]): oral damage

- caries
- teeth loss
- salivary gland swelling
- unstimulated salivary flow 0 ml/15 min

Table 17.6 Sjögren's Syndrome Damage Index (Barry *et al* [4]): systemic damage

neurological
- cranial neuropathy
- peripheral neuropathy
- other CNS pathology
- mononeuritis multiplex

renal
- nephrocalcinosis
- renal rubular acidosis
- glomerular filtration rate < 50% predicted
- proteinuria > 3.5 g/24 h
- end stage renal disease

pulmonary
- pleural fibrosis
- pulmonary fibrosis
- pulmonary hypertension

cardiovascular
- cardiomyopathy

gastrointestinal
- chronic pancreatitis

musculoskeletal
- erosive arthropathy

malignancy
- paraproteinemia
- other malignancy
- macroglobulinemia
- cryoglobulinemia
- lymphoma

4. APPENDIX: PREVIOUS SJÖGREN'S SYNDROME DISEASE ACTIVITY INDICES

Sjögren's Syndrome Disease Activity Index

Vitali *et al* developed in addition to the damage index the Sjögren's Syndrome Disease Activity Index (SSDAI).[2] The SSDAI consists of 8 defined items with scores ranging between 1 and 4 (see table 17.7).

Table 17.7 SSDAI: items of the Sjögren's Syndrome Disease Activity Index (Vitali *et al* [2])

	score
constitutional symptoms	
-fever	1
-fatigue	1
-change in fatigue*	1
change in salivary gland swelling*	3
articular symptoms	
- arthritis	1
- evolving arthritis*	1
hematologic features	
- leukopenia/lymphopenia (<3.5/<1.0x10^9/l)	1
- lymph node/spleen enlargement	2
pleurisy or pneumonia (not due to infection)	1
change in vasculitis*	3
active renal involvement	2
- any of: proteinuria*, increasing serum creatinin level above normal, nephritis*	
peripheral neuropathy (onset < 6 months)	1

* new or worsening

Sjögren's Systemic Clinical Activity Index

Bowman *et al* published in 2007 the Sjögren's Systemic Clinical Activity Index (SCAI).[3] The index measured 11 groups (see table 17.8). It is a very detailed questionnaire with about 65 (sub-)items that are scored in different ways, varying between scores between 0 and 4 (0: absent, 1: improving, 2: same, 3: worse; 4: new), yes or no, or with real test results.

The SCAI measures many features that are not independent such as items 26,27,28,29,31,32,33). Many others are not related to Sjögren's syndrome disease activity. Examples are Raynaud's phenomenon and blood pressure (items 13, 33, 34), a positive ANA (item 45), and antibodies to anti-SSA/Ro or anti-SSB/La (items 52 and 53). Paraproteins do no usually disappear when the disease becomes inactive. An acutely swollen major salivary gland (item 35) is usually due to secondary bacterial infection and not directly due to active disease. Bacterial parotitis is usually accompanied by abnormal items 37,38,43 and 44).

Table 17.8 SCAI: items of the Sjögren's Clinical Activity Index 29.01.07 (Bowman *et al* [3])

1. fatigue
constitutional
2. fever
3. swollen lymph glands/spleen
4. unintended weight loss > 5%
musculoskeletal
5. painful joints
6. early morning stiffness E 30 mins
7. swollen large joints (arthritis)
8. swollen small joints (arthritis)
score separately finger joints, MCP joints, wrists, elbows, ankles, feet & toes
9. generalized polyarthritis
10. muscle pain
11. objective weakness
12. myositis
skin/vasculitis
13. Raynauds
14. minor cutaneous vasculitis
15. major cutaneous vasculitis
16. mild SCLE
17. extensive SCLE (>60%/body + 4 limbs)
respiratory
18. shortness of breath
19. pleural-pericardial pain
20. pleural effusion
21. interstitial lung disease
neurological
22. sensory neuropathy < 6 months
23. sensorimotor neuropathy < 6 months
(or pure motor neuropathy)
24. cranial sensory/motor neuropathy < 6 months
25. CNS involvement < 6 months
renal
26. dipstick proteinuria
27. 24 hr protein
is proteinuria due to active nephritis
28. active urinary sediment
29. active nephritis with 3 months
30. nephrotic syndrome
31. serum creatinine
32. creat clearance/GFR mls/min)
33. systolic blood pressure
34. diastolic blood pressure
salivary gland
35. acutely swollen major salivary gland
haematology/other bloods
36. haemoglobin g/dl
37. total white cell count x 10^9/l
38. neutrophils x 10^9/l
39. lymphocytes x 10^9/l
40. platelets x 10^9/l
41. evidence of active haemolysis
42. Coomb's test positive
43. ESR (mm/hr)
44. CRP (units)
immunology
45. ANA
46. dsDNA
Crithidia pos/neg
47. C3
48. C4
49. IgG g/l
50. IgA g/l
51. IgM g/l
52. anti Ro (pos/neg & titre)
53. anti-La (pos/neg & titre)
54. cryoglobulins
55. paraprotein
ocular test
Schirmer-I test (abn ≤ 5 mm/5 min)
salivary test
unstimulated salivary flow rate
(abn ≤ 1.5 mls/15 mins)

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Latest additions or modifications (date: dd.mm.yyyy)

date	*addition/modification*
20.10.2009	major additions on fundamental aspects of scoring systems for disease activity, disease damage and symptoms
20.10.2009	ESSDAI scoring systems; ref 7
22.10.2009	rearrangement of paragraphs (pp 133-135)
07.02.2010	minor text corrections and additions

Associated and overlapping autoimmune diseases

18

Associated and overlapping diseases

Associated diseases are diseases that occur more often together in the same person than by chance. Overlapping diseases have common symptoms and/or signs and may be associated or not. For some overlapping diseases, such as sarcoidosis, there is no indication at all of an association or any other relationship than by chance (see box). This chapter is limited to associated diseases of which some may overlap with Sjögren's syndrome (table 18.1).

Table 18.1 Sjögren's syndrome: overlapping and associated autoimmune diseases

disease	*percentage*	
	in SjöS	*with SjöS*
rheumatoid arthritis	1-2	33
SLE		33
systemic sclerosis		33
MCTD		
antiphospholipid syndrome		
SCLE		
PBC		
Graves' disease		
Hashimoto's disease		
autoimmune hepatitis		
celiac disease		
myositis		
autoimmune pancreatitis		
primary sclerosing cholangitis		
atrophic gastritis		
pernicious anemia		
IC/BPS		
nonbacterial prostatitis		

SjöS: Sjögren's syndrome; SLE: systemic lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; MCTD: mixed connective tissue disease; PBC: primary biliary cirrhosis; IC/BPS: interstitial cystitis/bladder pain syndrome

Non-associated overlapping diseases

Overlapping features between Sjögren's syndrome and sarcoidosis may be enlargement of the salivay and tear glands, sicca symptoms, fatigue, fever, arthralgia, rthritis, leukocytopenia, ANA and reumatoid factor.

Some features only show superficial overlap as they can be clearly distinguished by further examination. The infiltration of salivary and tear glands in sarcoidosis is diffuse while in Sjögren's syndrome it is situated around the ducts.

Associated systemic diseases

Associated systemic diseases are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD) and systemic sclerosis. Sjögren's syndrome has overlapping features most clearly with SLE. In some patients it may be difficult or impossible to decide whether they have Sjögren's syndrome, SLE or both. In addition to the association in individual patients, associated diseases also occur more often in family members, with or without Sjögren's syndrome.

Associated organ specific disease

Examples of associated organ specific diseases are Graves' disease, Hashimoto's disease, primary biliary cirrhosis, subacute cutaneous lupus erythematosus (SCLE) and interstitial cystitis/bladder pain syndrome (table 18.1). Because of their organ specific nature, overlap of symptoms is rare and if present mainly concerns laboratory findings such as antinuclear antibodies (ANA). Of the associated organ specific diseases, the overlap of Sjögren's syndrome is most clearly with SCLE because of skin photosensitivity and antibodies to SSA/Ro and SSB/La.

Associated overlapping autoimmune diseases

In this section a description will be given of the way the associated diseases show overlapping features with Sjögren's syndrome.

Rheumatoid arthritis
Systemic lupus erythematosus
Systemic sclerosis
Mixed connective tissue disease
Antiphospholipid syndrome
Subacute cutaneous lupus erythematosus
Primary biliary cirrhosis
Graves' disease
Hashimoto disease
Autoimmune hepatitis
Celiac disease
Myositis
Autoimmune pancreatitis
Sclerosing cholangitis
Atrophic gastritis
Pernicious anemia
Interstitial cystitis/bladder pain syndrome
Nonbacterial prostatitis

this chapter is under construction

this chapter is under construction

Incomplete Sjögren's syndrome

19

There are many autoimmune diseases and each of them has at least one feature that is characteristic for the disease. This feature may be a single symptom or sign but is more commonly a combination of several symptoms and signs. Diseases can be recognized by their characteristic combination of features, the so-called "face" of the disease. This "face" plays a crucial role in the diagnostic process for the disease.

In addition to the characteristic (specific) features, there are many nonspecific features such as fatigue, (nonerosive) arthritis, myositis, Raynaud phenomenon and several abnormal laboratory findings (see the orange circle in figure 19.1) that occur in many auto immune diseases. The clinical relevance of these nonspecific features is highly variable. Nonspecifc features can be attributed to a particular disease if there is also a characteristic feature of the disease in question. This is illustrated by the red area in figure 19.2. In this example, typical features of Sjögren's syndrome are present in which case the accompanying nonspecific features such as fatigue or antinuclear antibodies (ANA) are attributed to Sjögren's syndrome as well. For nonspecific features that are treated differently depending on the disease to which they belong, additional investigations may be required to exclude a background other than Sjögren's syndrome.

Examples of this are arthritis and polyneuropathy where rheumatoid arthritis and diabetes mellitus have to be excluded respectively.

The next step may be to investigate whether the patient fulfils the diagnostic criteria for the most likely diagnosis, *e.g.* Sjögren's syndrome.[1] This is especially

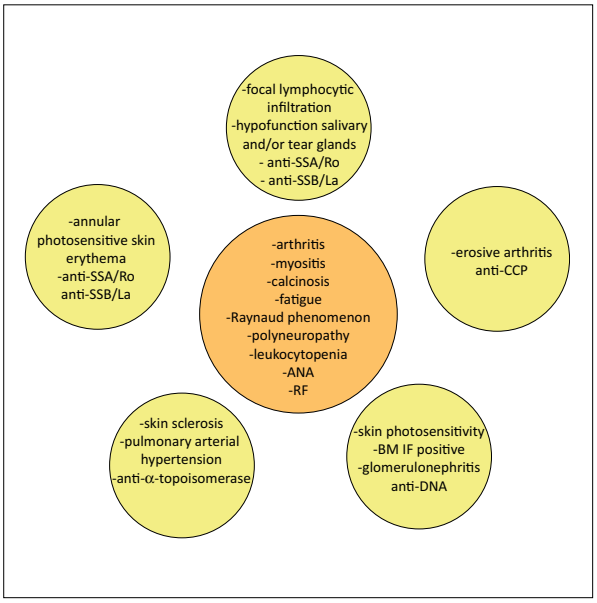

Figure 19.1 *Schematic representation of nonspecific (orange circle) and more or less disease specific features (yellow circles). None of the symptoms and signs are present in all patients with a particular disease. Abbreviations. CCP: cyclic citrullinated peptide; ANA: antinuclear antibodies; RF: rheumatoid factor; BM: basal membrane; IF: immunofluorescence.*

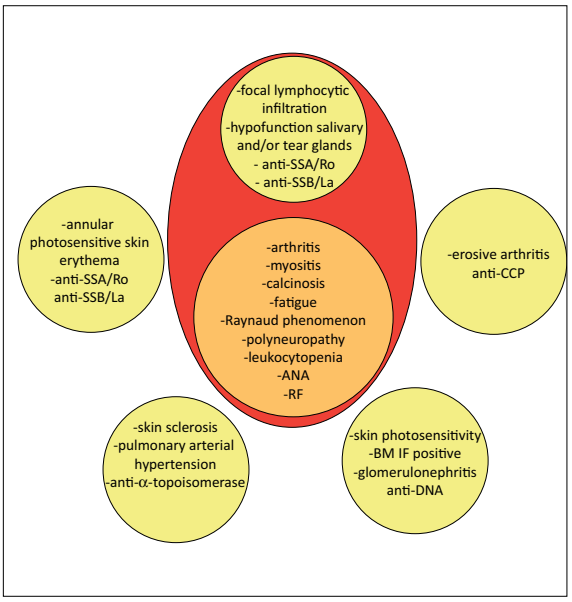

Figure 19.2 *Schematic representation of a particular combination (red area) of nonspecific and more specific features suggesting Sjögren's syndrome. Abbreviations: see legend of figure 19.1.*

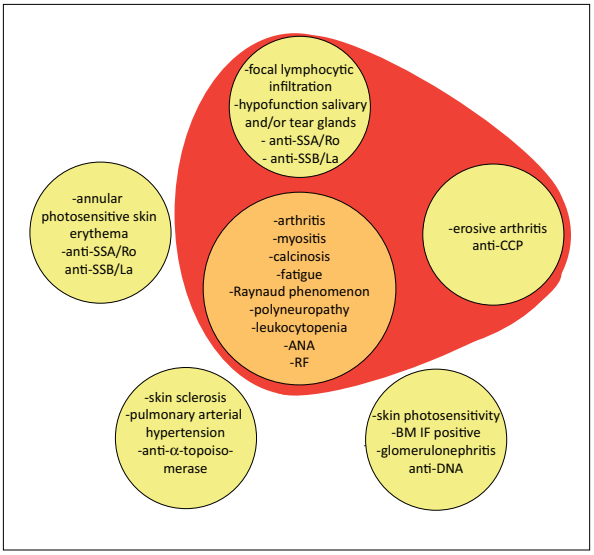

Figure 19.3 *Schematic representation of nonspecific (orange circle) and more or less disease specific features (yellow circles). Patients may have features of more than one disease, in this example Sjögren's syndrome and rheumatoid arthritis.*
Abbreviations: see legend of figure 19.1.

important if the patient takes part in a scientific study but may be redundant or even unethical in a clinical situation.

Patients may also have features that are compatible with two disease. This is illustrated in figure 19.3. It seems semantic whether the patient has one broad disease, two separate diseases or two overlapping diseases as nothing is really known about the cause of either disease. However, the disease in this example is usually classified as rheumatoid arthritis with secondary Sjögren's syndrome.

Undifferentiated connective tissue disease

Patients with signs and symptoms suggesting a systemic autoimmune disease but who lack a characteristic "face" and consequently do not fulfil the classification criteria for any defined disease, are common in clinical practice (table 19.1). The disease in these patients has been named "undifferentiated connective tissue diseases" (UCTDs).

The disease in patients with an undifferentiated onset may evolve to definite conditions, or remain indefinitely undifferentiated, or experience a remission of all pathologic features. However, about 70% of patients with an undifferentiated onset will not develop a defined systemic auto immune disease. The evolution to a defined systemic autoimmune disease occurs in the majority of cases within the first five years of disease. The clinical picture of stable undifferentiated connective tissue disease is mild and characterized by the absence of major organ involvement.

Table 19.1 Clinical and serological manifestations of undifferentiated diseases [1]

manifestation	*percentage*
arthralgia	37-80
Raynaud phenomenon	33-56
arthritis	14-86
leukopenia	11-41
xerophthalmia	7-41
xerostomia	12-36
photosensitivity	10-24
anemia	16-23
serositis	5-16
malar rash	6-13
oral aphtosis	3-27
thrombocytopenia	2-33

The laboratory profile of stable undifferentiated connective tissue disease is characterized by the presence of single autoantibody specificities.[2]

Incomplete Sjögren's Syndrome ("Sjögren-like syndrome")

It is quite common for a patient to fit well in the circle (or have the "face") of Sjögren's syndrome, with or without additional nonspecific features, but not to fulfil the diagnostic criteria for Sjögren's syndrome. In this situation, the disease can be classified as UCTD but the name "incomplete Sjögren's syndrome" or "Sjögren-like syndrome" may be more appropriate.[4] This is well illustrated by the study of Brun *et al.* [5] They found that only 40.9% of patients with an expert clinical diagnosis of Sjögren's syndrome fulfilled the criteria for Sjögren's syndrome (see chapter 4 for further details of this study). There are at least two possible explanations for this discrepancy.

As far as SLE is concerned, patients with less than 4 items of the criteria are often classified as *lupus-like syndrome*. However, the word *like* suggests a (confusable) similarity only and not that it is the same less extensive disease. Therefore, the addition of the word *incomplete* is more appropriate than the word *like.* This addition is proposed for patients with features of Sjögren's syndrome, no confusable disease but less than 4 items of the diagnostic criteria.

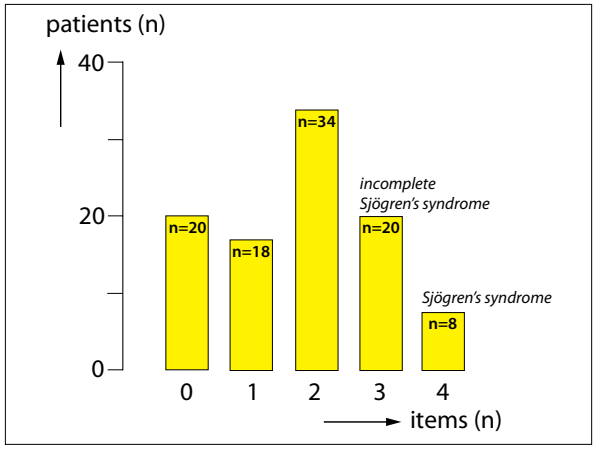

Figure 19.4 *Frequency distribution of the number of items of the European criteria for Sjögren's syndrome present in 100 patients with IC/BPS.*

Only 45% of Sjögren's patients according to the 1993 criteria fulfilled the 2002 criteria.

Ramos-Casals et al 2009 [8]

A similar low sensitivity of the 2002 criteria as compared to the 1993 criteria was found previously in prevalence studies.

Kabasakal et al 2006 [12]
Haugen et al 2008 [13]
Birlik et al 2008 [14]

It is shocking that there is no formal diagnosis for a large group of patients who fulfil the 1993 criteria but not the 2002 criteria for Sjögren's syndrome.

van de Merwe, see text below

The first may be that this is due to the fact that symptoms or signs do not always begin at the same time and that the patient will fulfil the diagnostic criteria at some point in the future. Clinical experience indicates that this will only happen in a minority of patients and that the majority will not fulfil diagnostic criteria even 10 or 20 years later.

A second explanation could be that any method of dividing patients into two groups (those with and those without Sjögren's syndrome using whatever decision rule), is very artificial implying that different rules will never give the same result.

Vaz *et al* analysed 184 patients with UCTD.[9] The patients of this group with antibodies to SSA/Ro and/or SSB/La (27% of the cohort) presented a higher prevalence of leukopenia and sicca syndrome but not of other clinical features suggestive of Sjögren's syndrome. These data prove that there is an intermediate group between healthy people and people with "full" (fulfilling the criteria) Sjögren's syndrome that has features that are characteristic of Sjögren's syndrome (sicca syndrome and antibodies to SSA/Ro and/or SSB/La). Based on data on the course of the disease in patients with UCTD,[2] the majority of them will probably not evolve to full Sjögren's syndrome. Such intermediate groups were found previously in patients with interstitial cystitis/bladder pain syndrome (see figure 19.4).[10,11] None of the intermediate patients has evolved to a differentiated connective tissue disease such as Sjögren's syndrom or SLE to date (*unpublished data*, J.P. van de Merwe).

Ramos-Casals *et al* [8] analyzed the clinical features of patients with a well-established diagnosis of primary Sjögren's syndrome according to the 1993 criteria [6,7] and tested whether they fulfilled the 2002 classification criteria.[1] The main difference between the 1993 and 2002 criteria is that the latter require 1. a positive salivary gland biopsy, or 2. the presence of antibodies to SSA/Ro and/or to SS-B/La. The serological item was also fulfilled in the 1993 criteria if a test for ANA or rheumatoid factor was positive. Only 286 (45%) of 507 Sjögren's patients according to the 1993 criteria fulfilled the 2002 criteria. A similar low sensitivity of the 2002 criteria as compared to the 1993 criteria was found previously in prevalence studies.[12-14]

Patients who did not fulfil the 2002 criteria ("1993-patients") were 4 years older at diagnosis (59 *versus* 55 years) than those who also fulfilled the 2002 criteria ("2002-patients"). No clinically significant differences were found in the prevalence of xerostoma, xerophthalmia, abnormal eye tests, and parotid scintigraphy. "1993-patients" had a lower frequency of arthritis (13 *versus* 20%), vasculitis (5 *versus* 10%), peripheral neuropathy (4 *versus* 13%), and cranial nerve involvement (0.5 *versus* 4%). The difference in the global percentage of patients with systemic involvement (42 *versus* 50%) was not statistically significant. "1993-patients" also had a lower frequency of raised ESR levels (16*versus* 30%), anemia (21 *versus* 35%), leukopenia (12 *versus* 19%), hypergammaglobulinemia (2 *versus* 14%), rheumatoid factor (29 *versus* 54%), and cryoglobulinemia (5 *versus* 10%). No significant differences were found in the development of B-cell lymphoma and in survival.

From these results it can be concluded that in addition to patients who fulfil the 2002 classification criteria for Sjögren's syndrome, another group exists of about the same size. These patients have similar local and systemic disease manifestations, and fulfil the 1993

See also Chapter 4 on the diagnosis.

criteria for Sjögren's syndrome but not those of 2002. It is shocking that there is no formal diagnosis for this large group of patients while it is crystal clear that they have the same disease as those who fullfil the 2002 criteria for Sjögren's syndrome.

Recently proposed diagnostic criteria for interstital cystitis/bladder pain syndrome show that the exclusion of patients with typical clinical features of the disease in question can be avoided by the introduction of various types of disease within the classification.[15] This allows that a single set of criteria with subtyping is useful in clinical practice as well as for scientific studies.

Keratoconjunctivitis sicca, focal lymphocytic sialoadenits and sicca syndrome

The diagnosis of Sjögren's syndrome is made on the basis of exclusion of diseases that may mimick Sjögren's syndrome (confusable diseases), such as sarcoidosis and lymphomas. In addition, positive findings are necessary, such as:[1]

- eye symptoms
- mouth symptoms
- swelling, duct abnormalities and lymphocytic infiltration of salivary glands
- diminished tear secretion
- diminished saliva secretion
- autoantibodies to SSA/Ro and/or SSB/La

Usually, for a diagnosis of Sjögren's syndrome, 4 items have to be documented. When patients do not fullfil the diagnostic criteria for Sjögren's syndrome and other diseases are excluded, it is likely in many cases that the disease is essentially the same as Sjögren's syndrome but with less manifestations (figure 19.5).

The Swedish opthalmologist Henrik Sjögren became famous because he recognized that some patients with *keratoconjunctivitis sicca* may have particular systemic features, a syndrome later described as Sjögren's syndrome. Other patients have typical eye and mouth symptoms without objective abnormalities, usually called *sicca syndrome*. Other patients have parotid swelling, an abnornal lip biopsy and antibodies to SSA/Ro and SSB/La, with no eye symptoms or abnormal eye tests for 20 or more years. This may be called *focal lymphocytic sialoadenitis.*

There is no scientific basis nor is it reasonable to consider these separate combinations of *features of Sjögren's syndrome* as diseases that have nothing to do with Sjögren's syndrome. The opposite seems more logical and more likely.

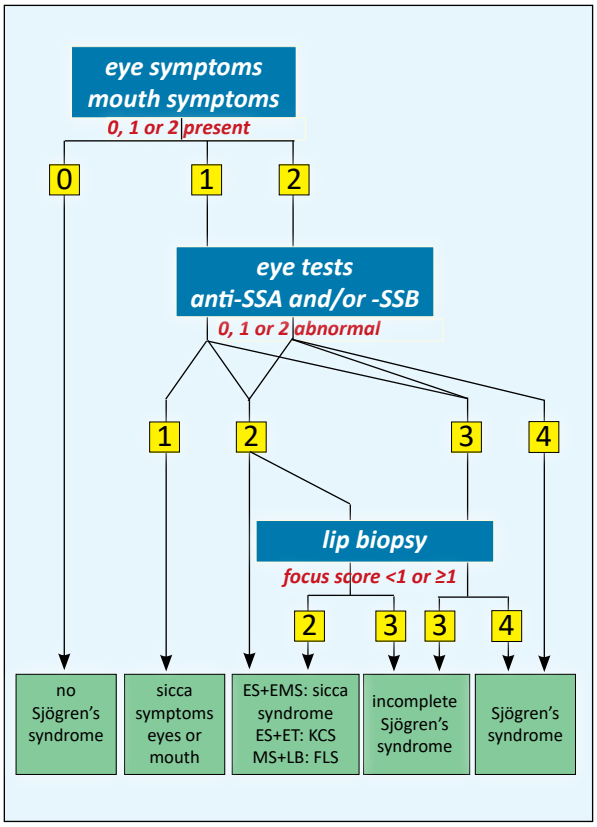

Figure 19.5 *Flow chart for the diagnosis of Sjögren's syndrome (see chapter on diagnosis for further details. The yellow squares show the number of criteria items present.*
Abbreviations: ES: eye symptoms; MS: mouth symptoms; ET: abnormal eye tests; LB: abnormal lip biopsy; KCS: keratoconjunctivitis sicca; FLS: focal lymphocytic sialoadenitis.

Conclusion

The presented data are compatible with the hypothesis that there is a continuous spectrum from *no disease* to *full-blown* Sjögren's syndrome. Any cut-off point for the diagnosis of Sjögren's syndrome is artificial in this situation and suggests that there are only two possible outcomes: *you have* Sjögren's syndrome or you *do not*. Application of a cut-off point in clinical practice is a self-fulfilling fallacy that causes a lot of harm for Sjögren's patients who do not fulfil the criteria.
The following list represents a simplified example of the possible continuum:

- no disease
- sicca symptoms of the eyes
  sicca symptoms of the mouth
- keratoconjunctivitis sicca
  focal lymphocytic sialo-adenitis

- Sjögren's like syndrome (3 items of the 1993 or 2002 criteria present)
- patients who fulfil the 1993 criteria but not the 2002 criteria for Sjögren's syndrome
- patients who fulfil the 2002 criteria for Sjögren's syndrome

Fulfilling diagnostic criteria without having the disease

The fact that not all patients who are considered to have a particular autoimmune disease by experts fulfil the diagnostic criteria for that disease is an unevitable consequence of making diagnostic criteria as specific as possible to avoid the enrolment of patients that do not have the disease under investigation. It is less well-known that the opposite may also occur: patients may fulfil diagnostic criteria without having the disease. This is illustrated in the next example.

Patient X with Sjögren's syndrome has the following manifestations of the disease:

1. fatigue
2. symmetric nonerosive polyarthritis
3. a daily feeling of dry mouth ≥3 months
4. a recurrent sensation of sand in the eyes
5. Schirmer test OD/OS: 3 and 4 mm
6. photosensitivity
7. leukocyte count: 3.2 x 109/l
8. antinuclear antibodies (ANA)
9. antibodies to SSA/Ro and SSB/La
10. rheumatoid factor 400 IU/ml;
    the anti-CCP test is negative

The patient fulfils the American-European criteria 1 for the diagnosis of primary Sjögren's syndrome on the basis of the manifestations 3,4,5, and 9. The other disease manifestations can also easily be attributed to Sjögren's syndrome: photosensitivity correlates with the presence of antibodies to SSA/Ro, 60-70% of Sjögren's patients have a positive ANA test, 10-15% has arthritis and 25% a low leukocyte count.

The patient also fulfils the ARA criteria for the diagnosis of systemic lupus erythematosus 3 on the basis of manifestations 2, 6, 7 and 8.

On the basis of the symmetric poly arthritis and the rheumatoid factor, a diagnosis of early rheumatoid arthritis could also be considered. However, the negative test for antibodies to CCP strongly argues against rheumatoid arthritis.[4]

Sjögren or SLE, or Sjögren and SLE?

Patients with primary Sjögren's syndrome may fulfil the diagnostic criteria of SLE without having SLE.

see text below

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Latest additions or modifications (date: dd.mm.yyyy)

01.08.2009	first version
20.08.2009	conversion to another DTP program
09.09.2009	more about negative effects of using cut-off point in diagnostic criteria in clinical practice
09.02.2010	paragraph added on keratoconjunctivitis sicca, focal lymphocytic sialoadenits and sicca syndrome; *idem* figure 19.5
27.02.2010	explanation that the term incomplete Sjögren's syndrome is more appropriate than Sjögren's -like syndrome (page 150).

Frequently asked questions 20

1. Is Sjögren's syndrome contagious?
No.

2. Is Sjögren's syndrome hereditary?
No, it is not hereditary. However, it does occur more commonly than normal in relatives of patients with Sjögren's syndrome.

3. Do you get Sjögren's syndrome through the wrong diet or lifestyle?
There is absolutely no evidence of this.

4. What is the life expectancy of a patient with Sjögren's syndrome?
Life expectancy is virtually normal. Risks are only higher if a patient also has special complications such as specific rare lung disorders or non-Hodgkin lymphoma.

5. Can you ever completely get rid of Sjögren's syndrome?
In principle no, but this does not mean that the symptoms will always remain the same. When treating Sjögren's syndrome, we quite often see an improvement in the symptoms. Some patients have scarcely any symptoms after a time.

6. Is vaginal dryness also part of Sjögren's syndrome and what can be done about it?
Yes, this is possible. Treatment is discussed in chapter 5.

7. Is it true that Sjögren's syndrome can worsen or improve without there being any apparent reason?
Yes, Sjögren's syndrome often takes an undulating course, with there being any clear cause for this.

8. Should a Sjögren's patient get pregnant?
Yes, but some medication should be stopped beforehand. If you have antibodies to SSA/Ro and/or SSB/La or antiphospholipid antibodies, this can cause certain risks for the baby (see chapter 11).

9. Should a Sjögren's syndrome patient travel by plane?
Yes, but ensure that you have sufficient water and eye-drops for the flight. The air in planes is very dry. Also take along (sugar-free) chewing gum, since this will help to combat ear problems (feeling of pressure, "muffled" hearing) due to a difference in air pressure in the aircraft and in your middle ear during take-off and landing. The Eustachian tube, which links the middle ear to the pharynx, only allows more air through when swallowing, yawning and chewing.

10.How can you cope with the dreadful problem of fatigue?
Sometimes a cause for the fatigue can be found such as anaemia or an underactive thyroid gland. If known causes have been excluded, the only option is to "learn to live with it". The best method is to spread activities throughout the day and the week and to avoid activities involving exertion that do not contribute to the quality of life. Be a bit egoistic where that's concerned. See also chapters 5 and 6.

11.I went to a doctor who did a test to check the amount of tear fluid (Schirmer test). This was normal and the doctor said that this showed that I don't have Sjögren's syndrome. Is this correct?
No, approximately 20% of patients with Sjögren's syndrome have a normal Schirmer test. The diagnosis of Sjögren's syndrome is based on a combination of signs and symptoms and no single specific sign or symptom is essential for the diagnosis. See also chapter 4 on criteria for the diagnosis of Sjögren's syndrome.

12.Is a lip biopsy essential for a diagnosis?
It depends. If there are both characteristic eye and mouth symptoms, the blood contains antibodies to SSA/Ro and/or SSB/La, the eye tests are abnormal and other causes of the signs and symptoms have been excluded, a definite diagnosis can be made without a lip biopsy. However, if there are no antibodies to SSA/Ro and/or to SSB/La, the lip biopsy is necessary to complete the diagnosis according to the Ameican-European diagnostic criteria of 2002. The value of a lip biopsy is much less than thought previously as both the specificity and sensitivity are

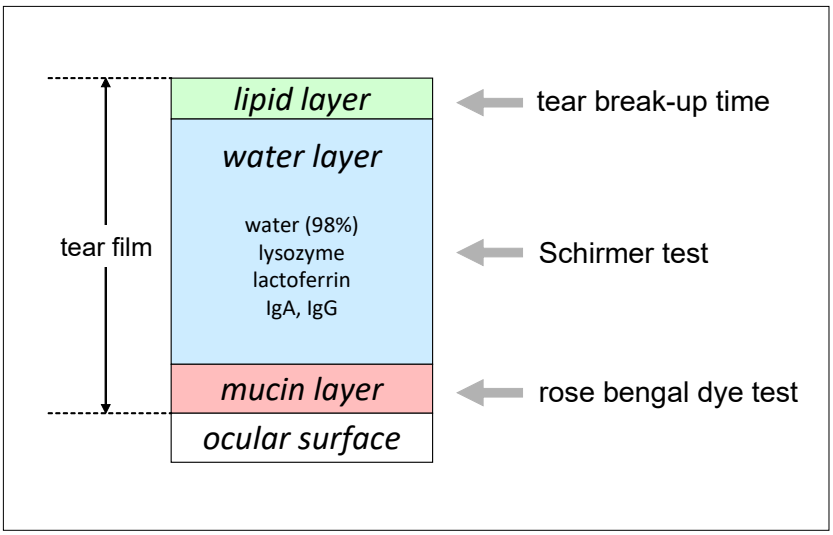

Figure 20.1 *The tear film consists of three layers, each with its own function. The outermost lipid layer provides a smooth surface (compare with a camera lens) and combats evaporation. The middle aqueous layer feeds the outermost eye cells and provides protection from infection. The innermost mucin layer ensures that the aqueous layer can adhere to the eye (cells normally repel water). The integrety of the lipid layer is tested with the tear braek-up time (BUT) and of the mucin layer with the rose bengal dye test. The Schirmer test measures the water layer.*

Figure 20.2 *Henrik Sjögren (1899-1986), the Swedish ophthalmologist whose name was given to the syndrome despite the fact that both Mikulicz and Hadden had described patients with the disease 45 years earlier.*

too low. On the other hand, the (lip) biopsy may be the only way to exclude certain complications of Sjögren's syndrome, *e.g.* a lymphoma. Furthermore, other diseases which affect the functioning of the salivary glands can sometimes be detected through a lip biopsy, *e.g.* sarcoidosis.

13.The eye specialist has done three tests: the Schirmer test, break-up time and the rose bengal staining test. Why are three tests necessary for the eyes and what do the results mean?
The fact that three tests need to be done is that individually the tests say too little to be diagnostic. The three above-mentioned tests each measure something different. The tear film consists of three layers (see figure 20.1): a lipid layer, an aqueous layer and a mucous layer.
The lipid layer is produced by the Meibomian glands in the eyelids. The aqueous layer is produced by the lacrimal glands and the mucous layer by the goblet cells in the conjunctiva.
The break-up time (BUT) is reduced by an impaired lipid layer, the Schirmer test by an impaired aqueous layer while the Rose Bengal test is positive if the mucous layer is impaired. Blepharitis is the most likely cause of the eye symptoms if the BUT is diminished and the other tests are normal.

14.What is "sicca syndrome"?
Sicca means dry. Sicca syndrome is used as a description for symptoms of eye irritation and dry mouth without it being possible to diagnose a disease. The name sicca syndrome suggests that the diagnosis is complete. It would be more accurate to refer to sicca symptoms or dryness symptoms without an objectifiable disease.
The majority of patients with sicca symptoms in whom it was not possible to diagnose Sjögren's syndrome, will not develop Sjögren's syndrome in the future.

15.What is Mikulicz's syndrome?
In 1888, Dr Mikulicz reported a patient with bilateral, painless swelling of the lacrimal and salivary glands and diminished production of tears and saliva. This combination of abnormalities was subsequently called Mikulicz's syndrome. Later, all kinds of diseases with swelling of the lacrimal and salivary glands were called by this name. Consequently, this name gradually became a repository for a variety of illnesses, including today's Sjögren's syndrome, certain forms of sarcoidosis, etc. This is precisely why the name is scarcely used anymore.

16.How long has Sjögren's syndrome been in existence?

Probably as long as human beings have existed. Back in 1888, Mikulicz reported a man with dryness symptoms of the eyes and mouth and swelling of the lacrimal and salivary glands. Also in 1888, Hadden described a woman with dryness symptoms of the eyes, mouth and skin. He treated this woman success fully with pilocarpine (!). After this, a number of patients were described in medical journals whom we now can assume to have had Sjögren's syndrome. But it was not until 1933 that Henrik Sjögren (figure 20.2), a Swedish opthalmologist, described 19 patients with keratoconjunctivitis sicca ("dry eyes"), 13 of whom also had joint inflammation. From that time onwards, the name Sjögren's syndrome was used, initially for the combination of kerato-conjunctivitis sicca, dry mouth and (rheumatoid) arthritis. Later, the definition of Sjögren's syndrome was changed into the combination of abnormalities of the lacrimal and salivary glands.

17.Is there any point in using pilocarpine if you have had Sjögren's syndrome for 20 years? Can the salivary and lacrimal glands still be stimulated?
Yes. The effect of pilocarpine is independent of the duration of the disease.

18.Can pilocarpine be used if you have both Sjögren's syndrome and interstitial cystitis (bladder pain syndrome)?
An undesirable effect of pilocarpine can be a need for more frequent urination due to contraction of the bladder muscles. So far, this does not appear to occur more frequently in patients with both Sjögren's syndrome and interstitial cystitis than in other patients with Sjögren's syndrome. At any event, it is no reason not to try it because if it should nonetheless lead to exacerbation of the bladder symptoms, you can always stop taking the pilocarpine.

19.Does pilocarpine have the same effect as saliva substitutes (sprays)? Is it advisable to change to pilocarpine? With whom should this be discussed?
Pilocarpine stimulates the production of your own saliva, including the constituents it contains to protect against infection. Artificial saliva substitute is some times no longer necessary if pilocarpine has the desired effect, but there is no objection to using both. You can discuss this with your general practitioner and/or your specialist who is treating you for your Sjögren's syndrome. Pilocarpine can also have a positive effect on the dryness of other mucous membranes, but is unfortunately not effective in all patients (see chapter 5).

20.Pilocarpine has only given me a moist nose. The dose was one capsule a day for three months. Is this correct?
The dose was too low. The optimal starting dose is 5 mg four times a day. Depending on the effect and on any side effects, the dose can be gradually increased to a maximum of 10 mg four times a day or 5 mg eight times a day. As a general rule, the likelihood of both desirable effects and undesirable (but harmless) side effects increases as the dose is increased and reduces as the dose is reduced. In the United States it is claimed that the effect of pilocarpine is some times only felt after a few months of usage.

21.Can a general practitioner prescribe pilocarpine?
Any medical doctor may prescribe pilocarpine. It may be worthwhile for the doctor to consult the pharmacist about this since some pharmacies refuse to supply pilocarpine in capsule form. The reason for this is that when capsules of 5 mg are made, one in a hundred capsules, for example, may contain 7 or 3 mg. From a medical point of view this is no problem, but the user needs to know this so as not to be surprised if one capsule has more or less (adverse) effects than another. The alternative is liquid form (less convenient) or the commercial preparation of pilocarpine (Salagen®). However, Salagen® is not reimbursed by health insurers in some countries. In - addition to the advantage of accurate dosage, Salagen® also has a second advantage of being absorbed more slowly into the body than capsules. This consequently reduces the chance of sweating attacks occurring 30 minutes after taking the pilocarpine.
Pilocarpine eyedrops should not be used for oral administration ("oral" = taking by mouth) because this is too inaccurate to be medically admissible.

22.Do you put on weight through taking pilocarpine?
No, or at most only indirectly due to an increase in your sense of taste and consequently in your appetite.

23.Patients with Sjögren's syndrome have a higher risk of developing non-Hodgkin lymphoma. When do you notice it, how can it be recognised, can it be caught in time, can it be detected at an early stage?
The likelihood of a patient with Sjögren's syndrome developing non-Hodgkin lymphoma (NHL) is 5-8% The NHL usually is a so-called MALT (Mucosa Associated Lymphoid Tissue) lymphoma. Certain patients have a higher risk than others, for example if the salivary glands are continually enlarged and if the patient has

antibodies to SSA/Ro and/or SSB/La.
Catching in time is not really the right expression because a lymphoma can only be diagnosed if it is already there. An alert doctor can at most diagnose it without needless delay. MALT lymphomas can, how ever, be successfully treated in virtually all patients. It is some times impossible to tell whether a tumour in a salivary gland or lymph node is malignant or not. Long-term use (5 or more years) of hydroxychlroquine (Plaquenil®) may possibly decrease the risk of MALT lymphomas. See also question 44.

24.Is it coincidence that several people in one family (aunt, niece) have Sjögren's syndrome?
No. Despite the fact that Sjögren's syndrome is not hereditary, it is known that hereditary factors play a role in the likelihood of developing the disease. The chance of a second close relative of a Sjögren's patient having the disease is approximately 12% (the normal chance for adults is about 0.4%).

25.If someone has dry eyes, dry mouth, dry tongue and osteoarthritis and the specialist says "it is not Sjögren's", what can it be?
Osteoarthritis has no connection with Sjögren's syndrome. Dryness can have many other causes such as diabetes, and underactive thyroid, high cholesterol and the use of certain drugs (see chapter 14). Whether the specialist is right or wrong depends on whether the correct tests have been carried out. Sometimes only a Schirmer test is carried out (measuring the amount of tear fluid with a filter paper) and if the result is normal the patient is told that he/she does not have Sjögren's syndrome. This conclusion is not justified because the Schirmer test is normal in 20% of Sjögren's patients.

26.Why is so little attention paid to acupuncture in Sjögren's circles? I receive 5-6 acupuncture treatments once a year from a medical acupuncturist and this gives me sufficient tear fluid for a year.
Acupuncture does not form part of "official" medicine, largely because no scientifically reliable study has been carried out into its possible effects. It should be remembered that acupuncture was the treatment used in China several thousand years ago. In today's China, Sjögren's patients are treated with the same drugs as in the western world, in addition to aditional Chinese methods of treatment.

27.Between what levels should the blood sedimentation rate of a Sjögren's patient fluctuate?
The erythrocyte sedimentation rate (ESR) depends on many factors, not only inflammation. Some Sjögren's patients have a high concentration of IgG antibodies in their blood or anaemia, resulting in an increase in the ESR. In many Sjögren's patients the ESR is either normal or only slightly increased (up to 40 mm for example). In the case of inflammation of the blood vessels (vasculitis), the ESR is often greatly increased, *e.g.* over 100 mm. The high ESR is in itself not dangerous, but is always caused by something.
See also the chapter 15 on clinical investigations.

28.Is there a connection between Sjögren's syndrome and thyroid disorders?
Yes, according to the literature 15% of patients with Sjögren's syndrome have or have had a thyroid disorder.

29. What causes gastrointestinal problems?
Gastrointestinal problems can have many causes which may or may not be related to Sjögren's syndrome. The clearest connection is with constipation, possibly because glands in the intestines produce less moisture, sometimes also due to the use of antiinflammatory drugs, the prostaglandin synthesis inhibitors (examples are aspirin, diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib but not Plaquenil®). See also the chapter on gastrointestinal disorders.

30. I am a forty year old woman and have had frequent attacks of cystitis during the past year. Antibiotics don't help.
Cystitis is usually caused by bacteria from the intestines, for example *Escherichia coli*. If the cystitis occurs frequently and is not improved by antibiotics, when the next attack of cystitis occurs it should be ascertained whether the urine contains white and/or red blood cells (indicating inflammation) and whether the urine contains bacteria, preferably by a urine culture (indicating bacterial infection). If a person has symptoms of cystitis, but it is not caused by a bacterial infection, this may indicate interstitial cystitis-bladder pain syndrome (IC-BPS). This is probably an autoimmune disorder of the bladder (see the chapter on urogenital disorders).

31. Can Sjögren's syndrome cause inflammation in the breasts?
There is a form of inflammation in the breasts caused by lymphocytes, known as lymphocytic mastopathy. This closely resembles the abnormalities that occur in the large salivary glands in patients with Sjögren's syndrome. However, lymphocytic mastopathy has

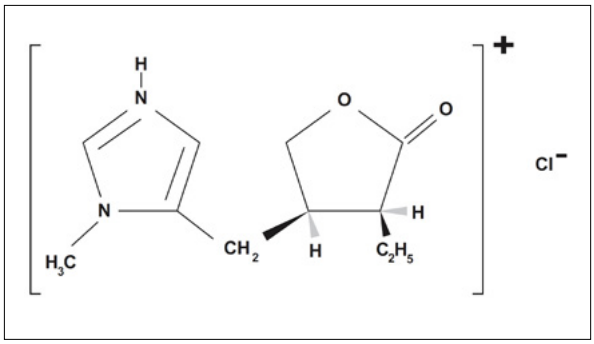

Figure 20.3 *The chemical formula of pilocarpine (hydrochloride or HCl).*

virtually only been described as a rare omplication in people with longstanding insulin-dependent diabetes mellitus. It has also been described in the case of systemic lupus erythematosus and hypothyroidism (underactive thyroid gland). Very recently, a patient with Sjögren's syndrome was reported with a non-Hodgkin lymphoma in the breast. Despite the fact that lymphocytic mastopathy has not been described so far in Sjögren's patients, it may be assumed that this is likely. It can be difficult, moreover, to distinguish between lymphocytic mastopathy and lymphoma.

32.What is the difference between pilocarpine and pilocarpine hydrochloride?
The official name of pilocarpine is pilocarpine hydrochloride or pilocarpine HCl for short (see fig. 20.3). The abbreviation HCl is often omitted and there is no difference. A similar situation also applies to many other drugs. Examples are: bromhexine (hydrochloride) and hydroxychloroquine (sulfate).

33.What is CREST syndrome?
CREST is an abbreviation of the five most important features of this generalised autoimmune disease:
C - Calcinosis (local calcium deposits in the skin)
R - Raynaud phenomenon
E - Esophagal dysmotility: abnormal movements of the muscles in the esophagus (UK oesophagus)
S - Sclerodactyly (thickening of the fingers)
T - Teleangiectasia (small collections of dilated blood vessels in the skin)
Patients with CREST often have anticentromer antibodies in their blood. The name CREST is replaced now by the name limited systemic sclerosis.

34.What is scleroderma?
Scleroderma (systemic sclerosis) is a group of generalised autoimmune disease characterised by skin abnormalities (including an increase in connective tissue). The skin tightens and in some patients the lung and kidney functions are impaired. Almost all patients also have Raynaud phenomenon. There are different forms of scleroderma with a different prognosis. The most severe form is diffuse systemic sclerosis ("diffuse scleroderma") involving the entire skin. This form is more often accompanied by lung and/or kidney disorders than the other forms.
In acroscleroderma, the skin lesions are limited to the

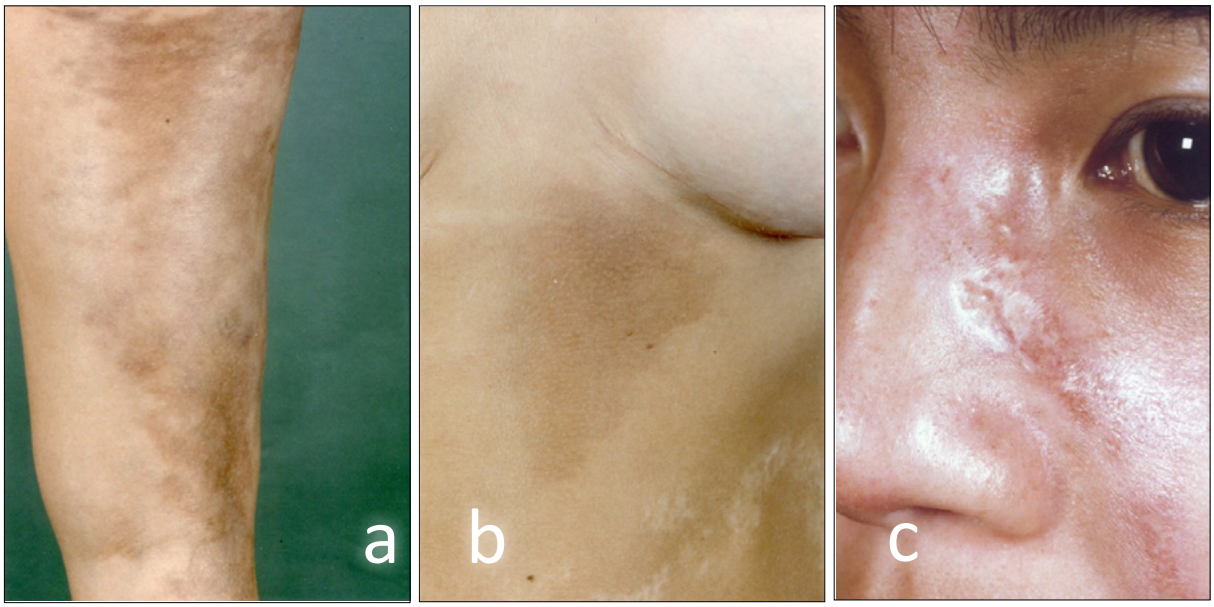

Figure 20.4 *Two types of (limited) scleroderma which are limited to the skin. a and b: morphea (back of the leg and breast, same patient); c: coup de sabre (on the nose).*

hands (and sometimes lower arms), feet (and sometimes lower legs) and nose. In morphea, the skin lesions are only found on certain areas of the trunk and/or limbs. The kidneys and lungs are not affected by this form of sclero derma. The skin lesions may also occur in linear bands and, due to the resemblance to a scar following a wound with a sharp instrument, this form is known as *coup de sabre*.

35.What is systemic lupus erythematosus?
Systemic lupus erythematosus (SLE) is a generalised autoimmune disease which more commonly occurs in women and non-white populations. The most common features are arthritis (joint inflammation), skin disorders (including a red butterfly rash on the face, see figure 20.5), sensitivity to sunlight, inflammation of the membranous sac around the heart (pericarditis) or of the pulmonary membrane (pleuritis), inflammation of the kidney (glomerulonephritis) and a low white blood cell count. The ANA (see chapter on clinical investigations) is positive and the anti-DNA in half the patients, particularly when the disease is active. The criteria for SLE are summarised in table 20.1. SLE can be diagnosed if four of the eleven items are present.

36.What is MCTD?
MCTD (Mixed Connective Tissue Disease) is a disease which forms a clinical overlap between systemic lupus erythematosus (SLE), myositis (inflammation of muscles) and systemic sclerosis (scleroderma). It is most likely a variant of SLE. On the basis of agreed criteria, in order to receive a diagnosis of MCTD a patient must have antibodies to RNP but not DNA.

Table 20.1 Summary of the criteria for the diagnosis of systemic lupus erythematosus (American Collega of Rheumatology 1997)

1. malar rash
2. discoid rash
3. photosensitivity
4. oral/nasopharyngeal ulcer
5. arthritis
6. pleuritis or pericarditis
7. proteinuria > 0.5 g/day
8. neurologic/psychiatric disorder
9. haematologic disorder
10. anti-DNA, anti-Sm, or antiphospholipid antibodies
11. antinuclear antibodies (ANA)[4]

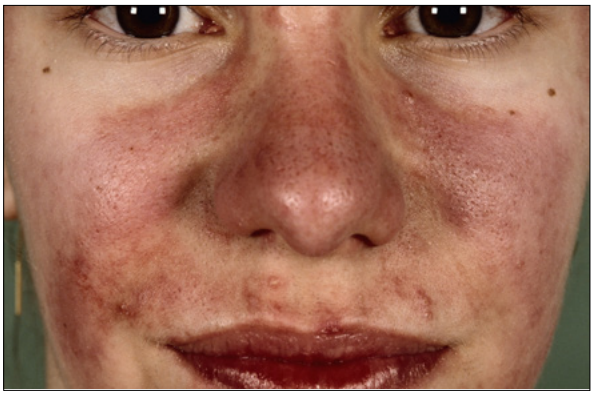

Figure 20.5 *The typical red butterfly rash of SLE.*

37.What is sarcoidosis and is there a link with Sjögren's syndrome?
Sarcoidosis or Besnier-Boeck disease is a disease which is sometimes difficult to distinguish from Sjögren's syndrome. In 90% of the cases, sarcoidosis shows clear abnormalities on a lung x-ray. Figure 14.6 shows the most typical feature on a lung x-ray. Tissue examination often reveals granulomas accumulations of a specific type of cell, surrounded by lymphocytes) (see figure 20.6 photo on the right). These abnormalities can also occur in lacrimal and salivary glands. In 10% of the patients, the lung x-ray shows no abnormalities. Sarcoidosis without lung abnormalities but with abnormalities in the lacrimal and salivary glands can be confused with Sjögren's syndrome. However, a lip biopsy in a patient with sarcoidosis shows diffuse lymphocytic infiltration and often the above-mentioned granulomas. Blood tests can also support the possibility of sarcoidosis such as elevated lysozyme, angiotensin-converting enzyme

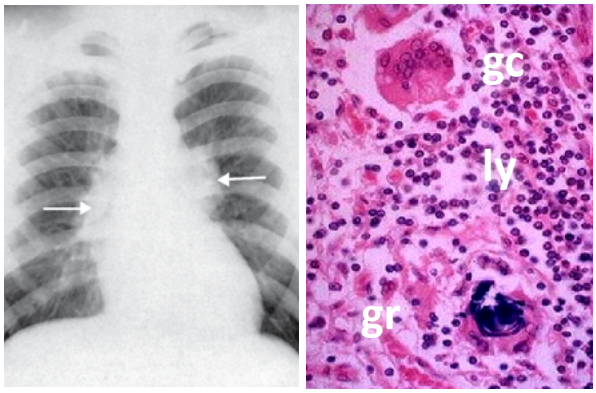

Figure 20.6 *Left: a lung x-ray showing the classic bnormalities of sarcoidosis: bilateral enlargement of the hilus glands (lymph nodes), see arrows; right: typical tissue abnormalities in sarcoidosis such as a granuloma (gr) surrounded by lymphocytes (ly) and a giant cell with multiple nuclei (mr).*

(ACE), calcium or vitamin D, which may occur in patients with sarcoidosis. Antibodies to SSA/Ro and SSB/La do not in principle occur with sarcoidosis (but do occur in 60-70% of the patients with Sjögren's syndrome).
There have recently been a number of publications reporting patients with both sarcoidosis and Sjögren's syndrome. Sarcoidosis occurs worldwide in an average of 1 per 5000 people, slightly more commonly in women than in men. The disease in more common in the negroid population and in Scandinavian countries (1:1600). 10-20% of known cases of sarcoidosis display no symptoms at all and the disease is only found by chance in a routine examination (*e.g.* a medical examination involving a lung x-ray). There must therefore be many people who "happen" to have both diseases. It is a simple matter to calculate that the chance of having both diseases in Scandinavian countries is 1:256.000 (Sjögren's syndrome 1:160; sarcoidosis 1:1600; chance of both 1 per 160x1600).

38.Does Sjögren-Larsson syndrome have any connection with Sjögren's syndrome?
No. Sjögren-Larsson syndrome (SLS) was first described in 1957 and consists of a combination of genetic ichthyosis (thickened fish-like skin), mental retardation and spastic paraplegia. SLS is an autosomal recessive genetic disease. Recessive means that the disease only occurs if two abnormal genes are present, one from each parent; autosomal means that the gene lies on one of the chromosomes 1-22, and not therefore on the 23rd gender-determining chromosome. The cause of the disease is a mutation (change) in the FALDH gene on chromosome 17 (FALDH is the abbreviation of Fatty Aldehyde DeHydrogenase), resulting in deficiency of the FALDH enzyme. Consequently metabolic products accumulate in the skin and nerve tissue.

39.Does Marinesco-Sjögren syndrome have any connection with Sjögren's syndrome?
No. Marinesco-Sjögren syndrome is a rare autosomal recessive genetic disease (see answer to previous question) with cataracts, cerebellar ataxia (balance and coordination impairment due to an abnormality in the cerebellum), mental retardation, muscle weakness, short stature and hypogonadism (impaired function of the reproductive glands). It is unknown which gene is defective.

40.Does Gougerot-Sjögren's syndrome have any connection with Sjögren's syndrome?
Gougerot-Sjögren's syndrome is the same as Sjögren's syndrome. This version of the name is only used in French-speaking countries.

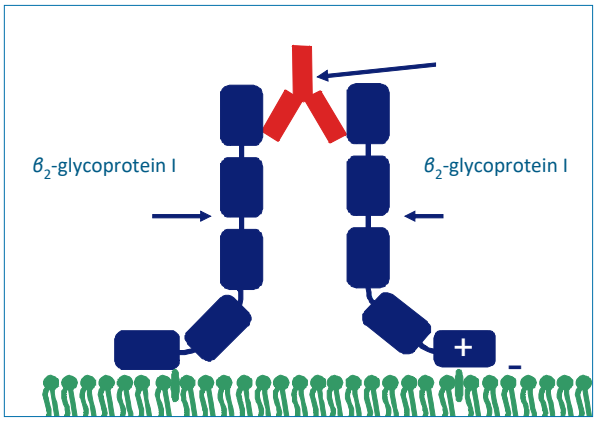

Figure 20.7 *The antiphospholipid antibodies interact with two β_2-glycoprotein I molecules. Via mechanisms that are not clarified to date, this binding leads to activation of endothelial cells and platelets and thrombosis.*

41.What is antiphospholipid syndrome?
Antiphospholipid syndrome (APS) is the combination of specific clinical features and laboratory diagnosis. The clinical features may be: thrombosis in veins or arteries or recurrent miscarriage. Many other features may be part of APS but are not included in the present diagnostic criteria such as low blood platelet count, livedo reticularis or aseptic necrosis of bone.
The laboratory features are anti phospho lipid antibodies (such as the lupus anticoagulant, anticardio lipin antibodies and antibodies to β_2-glycoprotein I). The physiological role of β_2-glycoprotein I is not known. Complexes of β_2-glycoprotein I and antibodies are not detected oin the blood. The antiphospho lipid antibodies interact with two β_2-glycoprotein I molecules. Via mechanisms that are not clarified to date, this binding leads to activation of endothelial cells and platelets and thrombosis (figure 20.7). [1]

There are three forms of APS.
a. people who have APS without any other autoimmune disease have primary APS.
b. APS associated with a generalised autoimmune disease such as SLE, SCLE, MCTD, systemic sclerosis or Sjögren's syndrome (so-called secondary APS).
c. there is also a form of APS associated with lupus-like syndrome.

Lupus-like syndrome is diagnosed if fewer than four items of the criteria for SLE are present (see table 20.1). By analogy with lupus-like syndrome, the term

Sjögren-like syndrome could be introduced for people with 1-3 items of the criteria for Sjögren's syndrome. It has been known for a long time that people with SLE sometimes have a positive syphilis reaction without having been in contact with the bacterium (*Treponema pallidum*) that causes syphilis. This is described as a false-positive syphilis reaction. It is now known that these false-positive reactions are caused by antiphospholipid antibodies.

42.I have the typical eye and mouth symptoms for Sjögren's syndrome and the Schirmer test is very low. However, the lip biopsy was normal. It this possible and have I got Sjögren's syndrome or haven't I?
A lip biopsy can be normal in Sjögren's syndrome, see also chapter 4 on diagnosis. Whether or not a diagnosis of Sjögren's syndrome can be made in this situation depends on other information (*e.g.* other abnormal findings, exclusion of other diseases which could cause the same symptoms and signs, *etc*). Occasionally the lip biopsy has not been correctly performed. It sometimes proved to have little or no salivary gland tissue and is therefore impossible to assess. Recent research has also shown that smoking can cause a lip biopsy to be negative.

43. I have Sjögren's syndrome and now BOOP has also been diagnosed. What is this and what connection does it have with Sjögren's syndrome?
Bronchiolitis Obliterans Organizing Pneumonia (BOOP) is called *organizing pneumonia* (OP) today. OP is a lung disease in which granulation tissue (scar tissue) causes narrowing or closure of the small branches of the respiratory tract (bronchioles). This lung abnormality has various causes, *e.g.* infections (adenovirus, cytomegalovirus, influenza, Legionella pneumophila), drugs (gold preparations, methotrexate, sulfasalazine), autoimmune diseases, transplantation and radiation.
If there is no association with another disease, the term *cryptogenic organizing pneumonia or* idiopathic OP is used. The course of the disease can vary per person. If the lung abnormalities increase, the patient is normally treated with prednisolone. In three-quarters of the patients the OP will then completely disappear, but 5% of patients die from the disease. Patients with the idiopathic form often recover following treatment with the antibiotic erythromycin. In the literature, 5-10 patients have been described with Sjögren's syndrome and OP. The relationship is uncertain and probably indirect. See also the chapter on pulmonary disorders.

44. Patients with Sjögren's syndrome have a higher risk than normal of getting a lymphoma. What are lymphomas?
Lymphomas are malignant growths mainly consisting of lymphocytes, specific white blood cells (see chapter 15). There are two main categories: Hodgkin lymphoma and non-Hodgkin lymphomas. It is only non-Hodgkin lymphomas (NHL) which occur more frequently than normal in Sjögren's syndrome.
A NHL occurs if lymphocytes (B-lymphocytes, T-lymphocytes or NK cells) undergo a change from normal cells to malignant cells which are capable of uncontrolled growth and spreading. The malignant cells divide so as to form identical copies (clones). Most (85%) of NHL come from B-lymphocytes at some stage of their development.
Lymphomas can occur anywhere in lymphatic tissue, such as lymph nodes, in intestines and in central nervous system. Symptoms depend on where they occur. In a lymph node this is swelling of the node. In addition, there may be other general symptoms such as fever, fatigue, night sweats, weight loss or itchy skin.
The diagnosis is based on examination of tissue, often a biopsy. Imaging is used to determine the location and spread. There are almost 40 different types of NHL. 13 of these types represent 90% of cases in the western world. With regard to the spreading of NHL, the following four stages are differentiated:

stage I:	disease in only one lymph node
stage II:	disease in a number of lymph nodes on one side of the diaphragm
stage III:	disease in lymph nodes above and below the diaphragm
stage IV:	the disease is also found outside the lymph nodes

Treatment depends on the type of NHL, the size and spread of the tumour and can vary from watch and wait with close monitoring, radiation therapy, chemotherapy, immunotherapy to stem cell transplantation. Patients with Sjögren's syndrome have a 44x increased risk compared to other people of developing NHL. The percentage of Sjögren's patients who develop NHL is 5-8%. NHL associated with Sjögren's syndrome are usually MALT lymphomas. MALT is an abbreviation of Mucosa-Associated Lymphoid Tissue. These lymphomas are slow growing B-cell lymphomas. In around half the cases the lymphomas occur in the salivary glands. After treatment, the prognosis for MALT lymphomas is generally speaking much better than for other types of lymphoma.

Table 20.2 Composition of a number of types of "artificial tears"

main ingredient	*preservative*	*(brand)name*
carbomer	thiomersal	Dry Eye® eye gel
	thiomersal	Thilo Tears® eye gel
	cetrimide	Vidisic® eye gel
dextran 70/hypromellose	polyquaternium-I	Duratears® eye drops
hyprolose	none	Lacrisert®
hypromellose	benzalkoniumchloride	hypromellose eye drops
	none	Hypromellose Monofree
hyaluronan ("hyaluronic acid")	none	Hylo-comod®
		Hyabak®
methylcellulose	thiomersal	methylcellulose eye drops
polyvidon	none	Duratears Free®
	benzalkoniumchloride	Oculotect® eye drops
	none	Oculotect Unidose® eye drops
	none	Protagens Mono 2%®
	benzalkoniumchloride	Protagens® eye drops
	cetrimide	Vidisic PVP Ophtiole® eye drops
polyvidon/polyvinylalcohol	chlorbutanol	Tears Plus® eye drops
	none	Tears Plus Unit Dose® eye drops

45.There are many types of artificial tears available. What is the difference between the different brands? Which are the best and how often should you use them?
Artificial tears are watery solutions to which an ingredient is added to give them greater viscosity (stickiness) so that they will adhere better to the eye. The differences between the different products lie between the added ingredients and the addition of preservatives. This latter aspect is important if a specific preservative cannot be tolerated. Eye gels have a higher viscosity than artificial tears. Artificial tear inserts dissolve slowly and consequently are effective for a long time. Table 20.2 gives an overview of a number of types of artificial tears and eye gels. In addition, there are eye drops which contain medication such as an anti-inflammatory or anti-allergy agent, *etc*. These should only be used if there is a special reason.
The choice between the different drops, gels and inserts can only be made by the user, in other words a question of trying them out. Generally speaking, the worse the eye disorder, the more watery the artificial tears need to be. An insert can only be used if there is sufficient tear fluid during the day to dissolve it. If this is the case, 1 insert per day is often sufficient.
The drops should preferably be used no more than 4-6x per day. With this frequency, the preservative is not harmful (unless it cannot be tolerated). It is even better to use preservative-free artificial tears, but these are relatively expensive and may be not or only partially be reimbursed. Only use artificial tears if they really help your eye symptoms. Eye symptoms can increase if eye drops are used too often, since this causes the last remaining protection against infection from your own tears to be washed away.

46. Since Sjögren's syndrome is an inflammatory condition, why can it not be treated with penicillin or something similar?
Inflammation is the body's response to tissue damage. Tissue damage can have different causes, such as mechanical (*e.g.* a cut), heat (burn), cold (frostbite), radiation or infection. Infection is the spreading and

Some artificial tears are available preservative-free in special bottles (Comod system). Once the bottle has been opened, the artificial tears will keep for 3 months.

multiplying of a micro-organism (*e.g.* bacterium, virus or fungus) in living tissue. If this causes disease, it is called an infectious disease. Treatment with penicillin or some other antibiotic has no point unless the inflammation is caused by a bacterial infection.

47. Can Sjögren's syndrome cause stones in the salivary glands?
There is no evidence that Sjögren's syndrome is more likely to lead to stones in the salivary glands than normal.

48. Do patients with Sjögren's syndrome have more likelihood of developing a tumour in the salivary glands?
Tumour means nothing more than swelling and a swelling can be benign or malignant. As is wellknown, some Sjögren's patients have unilateral or bilateral swelling of the salivary glands. In this sense, they have tumours in the salivary glands more frequently than normal. But this question is probably referring to malignant tumours such as cancer or malignant lymphomas. The only malignant disorders of the salivary glands in Sjögren's syndrome that occur more commonly than normal are non-Hodgkin lymphomas (see also answer to question 44).

49. What is the difference between thirst and a dry mouth?
Thirst is a sensation which is normally felt if the body dehydrates. Thirst ensures that we drink. Once the body has received sufficient liquid, the thirst sensation subsides again.
A dry mouth is caused by dryness of the surface of the mucous membranes in the mouth. Drinking helps as long as the liquid is present on the mucous membranes, a clear difference from thirst. If you have a dry mouth, you usually need to drink when eating dry food. There are different causes of thirst (see table 20.3).

Table 20.3 A number of causes of thirst

- physical exertion
- dehydration (diarrhoea, vomiting, heat, infection, diuretics)
- hormone disorders (e.g. overactive thyroid)
- diabetes mellitus
- diabetes insipidus (see box below)
- antihistamines, alcohol, caffeine, marihuana
- high sodium level in the body
- brain damage
- psychogenic

Diabetes insipidus

Diabetes insipidus is a disease in which the pituitary gland produces too little ADH (antidiuretic hormone). This may have a variety of causes and some forms are considered to be an autoimmune disease. The result is that the kidney cannot concentrate the urine, resulting in voiding of a great deal of dilute urine and extreme thirst.

Thirst is a common symptom of diabetes mellitus and not of Sjögren's syndrome. Sjögren's syndrome is characterised by dry mouth (and dryness of other mucous membranes).

50. Can a patient with Sjögren's syndrome have dental implants?
Yes, Sjögren's patients do not differ from other people in this respect. This is important because the likelihood of dental problems is much higher than normal in patients with Sjögren's syndrome. It is only if the patient is using drugs which greatly suppress the immune system that there are likely to be more problems with attachment of the implant to the bone. Implants need to be looked after and this is especially the case in people with insufficient or abnormal saliva. The question as to whether implants will be the solution for an individual person can only be answered by the dentist treating that person.

51. Is it true that the amount of saliva you produce decreases as you grow older?
Yes and no. It is true that older people on average produce less saliva than younger people. However, this has nothing to do with age but is simply caused by the fact that elderly people are more likely to have illnesses or use medication which causes less saliva to be produced.

52.What is the difference between Raynaud phenomenon and Raynaud disease?
A number of diseases and situations are known in which Raynaud phenomenon can occur. These may be autoimmune diseases (*e.g.* systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome), diseases leading to narrowing of the arteries, pulmonary hypertension (high blood pressure in the pulmonary arteries), neurologic disorders (*e.g.* disorders of intervertebral discs, tumours of the spinal cord, carpal tunnel syndrome), blood diseases which make the blood more viscous, damage due to repetitive movement (*e.g.* frequent

use of heavy drilling machine, playing the piano) and use of certain drugs (*e.g*. ergotamines and beta-blockers).
If Raynaud phenomenon occurs without one of these known situations or diseases being present, the condition is called primary Raynaud phenomenon or Raynaud's disease. On the basis of this classification, over half the people with Raynaud phenomenon have Raynaud disease.

53. Is it helpful to keep to a special diet for Sjögren's syndrome?
No. The same applies to Sjögren's patients as to everyone: eat healthy food with sufficient variation and fresh products. Many patients realise themselves that they can better avoid highly spiced or acid food because this can cause mouth complaints. Since quite a number of patients suffer from constipation, high-fibre food is important, but that also really applies to everyone.

54. Can I improve my resistance through diet, food supplements or extra vitamins?
Not really. Resistance mainly concerns the ability to avoid getting ill when infected by viruses or bacteria. So you can have resistance to virus A or bacterium B. The term resistance refers to the combination of all ways in which we prevent or fight infectious diseases. If you eat a healthy diet, there is usually no point in taking extra vitamins. There are a number of exceptions to this rule. In the Netherlands, people with a dark skin often produce insufficient vitamin D because Dutch sunlight is too weak for them. Extra vitamin D may be necessary for them. Many people with white skins have been found to have a vitamin D deficiency as well. Always discuss vitamin D treatment with your doctor.

55.May I take pilocarpine by putting a few drops from a bottle of pilocarpine eye drops in a glass of water?
No, absolutely not. The quantity of pilocarpine that you would swallow in this way is insufficiently accurate and can lead to severe overdosing.
Eye drops with pilocarpine are used to treat certain forms of glaucoma (increased eye pressure) and are not suitable for the treatment of eye complaints in Sjögren's syndrome.
Permissible forms of taking pilocarpine for Sjögren's syndrome are:

- oral mixture prepared by the pharmacy: accurate but inconvenient
- capsules prepared by the pharmacy: moderately accurate, but convenient
- commercial tablets (Salagen®): accurate, convenient, not reimbursed by health insurers in some countries

56.I have osteoarthritis. Should I now take calcium tablets?
There is no point in taking calcium tablets for osteo-arthritis unless you have osteoporosis and/or obtain too little calcium from your diet. There is a misunderstanding behind this question concerning the terms osteoarthritis (wear and tear of joints) and osteoporosis (loss of mineral density of bone tissue).
Osteoarthritis is a chronic condition characterised by the softening and breakdown of cartilage in the joints. This leads to a reaction by the underlying bone, causing the growth of new cartilage and bone. Over a period of time osteoarthritis gradually increases, causing pain and limited motility of the joints.
Osteoarthritis is the most common joint condition with the likelihood of developing it increasing with age: in 1% of the population under the age of 30 years to more than half the population over the age of 50 years. There are different types of osteoarthritis and specific risk factors.
Obese people are more likely to get osteoarthritis and less likely to get osteo porosis. Damage to joints also gives a higher risk of osteoarthritis. Long-term repetitive stress to certain joints in certain professions also increases the risk of osteoarthritis in these joints. There is no known treatment which slows down the progression of osteo arthritis. Treatment therefore consists simply of alleviating the symptoms (physiotherapy, painkillers) and if necessary dealing with known risk factors (*e.g*. obesity).
Osteoporosis is characterised by low bone mineral density and an increased risk of bone fractures. There are also specific risk factors for osteoporosis, such as being Caucasian, a history of osteoporosis in close blood relatives, smoking, excessive alcohol consumption, vitamin D deficiency, low dietary calcium intake, slight body build, too little exercise, early menopause, low testosterone level, use of corticosteroids (*e.g.* prednisolone) and diseases such as rheumatoid arthritis, an overactive thyroid (hyper thyroidism) and anorexia. Treatment generally consists of correcting all risk factors where possible and use of drugs which combat bone loss.

57.One of my pupils is larger than the other and does not respond to light. Has this anything to do with Sjögren's syndrome?
You probably have an Adie pupil. This is a harmless

A glossary of medical terms 21

acetylcholine
a substance that relays impulses to the nervous system

acetylcholine receptor
a structure on a cell that can bind itself specifically to acetylcholine

achlorhydria
absence of hydrochloric acid in the stomach

acidosis
a condition in which the tissues of the body are too acid

acute-phase protein
proteins that increase in concentration during inflammation

amylase
an enzyme that can break down starch, mainly produced by the salivary glands and pancreas

antigen
a substance against which the immune system can form antibodies or make T-lymphocytes which can specifically react with this antigen

antinuclear antibodies (ANA)
antibodies which are targeted against components in the nucleus of the cell

apoptosis
programmed death of cells of the body without this leading to an inflammatory response

autoimmune disease
a disease believed to be caused by the immune system

biopsy
excision and microscopic examination of a piece of tissue

blepharitis
inflammation of the eyelid due to blockage of Meibomian glands openings

bronchitis
inflammation of the airways

bronchitis sicca
inflammation of the airways caused by dryness of the mucous membranes

Candida albicans
a single-cell fungus (yeast)

carpal tunnel syndrome
the complex of symptoms that occur as a result of compression of median nerve in the wrist

cevimeline
a drug with the effect of binding to the muscarinic M3-receptor, comparable to pilocarpine

chloroquine
the generic name of the drug Nivaquine®; see also hydroxychloroquine

coeliac disease
an immune-mediated disease of the small intestine, also known as sprue

colitis
inflammation of the large intestine; see also ulcerative colitis

complement
a collective name for certain proteins (complement factors) which play an important role in the immune system

corticosteroids
steroid hormones produced in the adrenal cortex

C-reactive protein (CRP)
an acute phase protein (see above) of which the

concentration is increased by inflammation

CREST syndrome
an autoimmune disease belonging to the systemic sclerosis ("scleroderma") group; the name is replaced now by the term limited systemic sclerosis; CREST is the abbreviation for 5 possible manifestations of the disease:
C: calcinosis (local calcium deposits in the skin)
R: Raynaud phenomenon
E: esophagal dysmotility (abnormal movements of the esophagus)
S: sclerodactily (thickening and tightening of the skin of the fingers)
T: teleangiectasia (small collections of dilated blood vessels on the skin)
anticentromer antibodies in the blood are another typical feature of the disease.

cryoglobulins
cryoglobulins are complexes of mainly antibodies which form a gel at low temperatures and can consequently make the blood thicker (more viscous)

cystitis
bladder inflammation (see also inflammation and infection)

cystoscopy
examination of the inside of the urinary bladder using a (flexible) viewing instrument (cystoscope)

dacryoadenitis
inflammation of the tear-producing (lacrimal) gland

diabetes mellitus
sugar diabetes

erythrocyte
red blood cell

ESR
erythrocyte sedimentation rate, a blood test to detect inflammation

etiology
the cause of a disease

exanthem
red rash

first-degree relative
the parents, brothers, sisters, or children of an individual

fibromyalgia
a poorly understood disease with pain in the muscles, ligaments and tendons without signs of inflammation

focal lymphocytic sialoadenitis
inflammation of the salivary glands with local accumulation of lymphocytes around the ducts, a feature of Sjögren's syndrome

focus
a general term with a special meaning in the description of the histology of salivary gland biopsies: an accumulation of 50 or more lymphocytes

focus score
the number of foci (see focus) per 4 mm^2 in salivary gland tissue

gastritis
inflammation of the (mucous membrane lining the) stomach

glomerulonephritis
inflammation of the kidney filter system

glucose
sugar

heart block
decreased conduction speed in the heart resulting in a slow heart beat; it is a possible symptoms of neonatal lupus, a disease of the foetus or newborn caused by antibodies to SSA/Ro from the mother

haemoglobin
a colouring substance in the red blood cells; measurement of the concentration of haemoglobin in the blood is a test of the presence of anaemia

HLA
HLA is the abbreviation for Human Leukocyte Antigen, a reference to the white blood cells on which they were first discovered. They are also known as transplantation antigens because they play a role in the rejection of transplants.

Hunner's ulcer (or lesion)
a lesion in the bladder that can occur in interstitial cystitis (bladder pain syndrome); the name is misleading as it is not an ulcer; the prevalence is severely underestimated while the presence has

major impact on treatment

hydroxychloroquine
the generic name for the drug Plaquenil®

hypergammaglobulinemia
an excessive concentration of immunoglobulins ("antibodies") in the blood

hyperthyroidism
overactive thyroid

hypothyroidism
underactive thyroid

hyperventilation
breathing too rapidly and/or too deeply, resulting in too much carbon dioxide being breathed out and an increased of the pH in the body

hyperviscosity
an increase in the viscosity (thickening or stickiness) of the blood

immune complex
a complex or cluster of antibodies, antigen and complement

intrinsic factor
a protein (glycoprotein) formed by the stomach that is necessary for the absorption of vitamin B12 in the small intestine

IgA
a class of antibodies that is supposed to protect the mucous membranes of the body

IgE
a class of antibodies that may increase in number in certain allergic reactions

IgG
a class of antibodies found in high concentration in the blood and can penetrate all body tissues

IgM
a class of antibodies mainly present in the blood

immunoglobulins
a general name for antibodies without indicating what the antibodies are targeted against

incidence
the number of new cases of a disease per year; see also prevalence

infection
the dissemination of microbial agents such as bacteria and viruses in the body; many infections have a subclinical (no signs of disease) course while other cause disease

inflammation
the body's reaction to tissue damage, classically consisting of pain, redness, swelling, increased (local or general) temperature and loss of function; inflammation has many different causes such as physical or chemical trauma, radiation, immune reaction or infection

interstitial cystitis (bladder pain syndrome)
a chronic inflammation of the urinary bladder; the symptoms are similar to bladder inflammation due to a bacterial infection of the bladder ("cystitis"); the cause of interstitial cystitis is unknown

interstitial nephritis
inflammation of the kidney tubules

irritable bowel syndrome
also known as "spastic colon" or "mucous colitis", a condition with recurrent abdominal pain with constipation and/or diarrhoea

keratoconjunctivitis sicca
inflammation of the front of the eye (conjunctiva and cornea) which also forms part of Sjögren's syndrome

leukopenia or leukocytopenia
a decrease in the number of white blood cells

lip biopsy
excision and microscopic examination of small salivary glands from the inside of the lip

lissamine green
a dye which can be use for eye tests instead of rose bengal

livedo reticularis
mottled discoloration of the skin; a possible symptom of antiphospholipid syndrome

lung embolism
also called pulmonary embolism; thrombosis in a blood vessel of the lungs

lupus anticoagulant
an antiphospholipid antibody which can cause thrombosis

lymphocytic interstitial pneumonitia (LIP)
inflammation of the lungs in which lymphocytes accumulate around the small airways

lymphocytes
specific white blood cells, which may be subdivided *e.g.* as B-lymphocytes and T-lymphocytes

maculopathy
a disorder of the retina which may be caused, for example, by long-term overdosing with (hydroxy)chloroquine

MALT lymphoma
a lymphoma caused by lymphocytes in or near mucous membranes (MALT = mucosa associated lymphoid tissue)

MCTD
an autoimmune disease (abbreviation for mixed connective tissue disease), a variant of systemic lupus erythematosus

Meibomian glands
the Meibomian glands are situated in the eyelids and produce oily secretions which combat evaporation of tear fluid, for example; blockage of the Meibomian glands can result in blepharitis (see above)

monocytes
specific white blood cells; monocytes may undergo changes and migrate to the tissue, so-called macrophages; they play an important role in ingesting and breaking down particles such as bacteria which are then offered to lymphocytes; they also play a role in inflammatory reactions

monoclonal
antibodies are described as monoclonal if they are derived from identical B-lymphocytes; high concentrations of monoclonal antibodies may occur in Sjögren's syndrome and some malignant diseases such as Waldenström's macroglobulinemia and multiple myeloma

muscarinic receptor
one of the acetylcholine receptors, found e.g. in salivary and lacrimal glands

myasthenia gravis
an autoimmune disease which is caused by antibodies to the nicotine receptor for acetylcholine on skeletal muscles

myositis
inflammation of muscles

nerves
facial nerve: the 7th cranial nerve
trigeminal nerve: the three-branch nerve, the 5th cranial nerve

NSAID
a collective name for certain anti-inflammatory drugs; an abbreviation for non-steroidal anti-inflammatory drugs that indicates that they do not contain corticosteroids

oligoclonal
the presence of several monoclonal groups of antibodies; see also monoclonal and polyclonal

osteoporosis
loss of density and structure of bony tissue; the effect of various risk factors accumulate; examples of risk factors for osteoporosis are:
- having family members with osteoporosis
- vitamin D deficiency (very common !!)
- insufficient intake of calcium
- old age
- smoking
- excessive alcohol consumption
- inactivity
- menopause
- using corticosteroids
- having a disease such as hyperthyroidisms, celiac disease, inflammatory disease such as rheumatoid arthritis or inflammatory bowel disease and mastocytosis

pancreas
a gland that lies behind the stomach and secretes enzymes involved in digestion

pancreatitis
inflammation of the pancreas

parotid gland
the large salivary gland situated in front of each ear

parotitis

inflammation of the parotid salivary glands

polyclonal
the presence of a group of antibodies derived from many lymphocytes (the normal situation)

polymyositis
a disease in which several muscles are inflamed; it can also form part of a generalised autoimmune disease

prevalence
the part or percentage of the population in which a specific disease occurs; see also incidence

Raynaud phenomenon
a condition in which the hands and/or feet turn to white-blue in the cold and often to turn red when they warm up

retina
lining of the interior of the eye

retinopathy
disorder of the retina

rheumatoid factor
an autoantibody (usually of the IgM class) to the Fc part of IgG; see chapter 15

rose bengal dye
a red dye that colours cells of the eye that are not covered by mucin

saliva flow
the amount of saliva produced in 15 minutes

sarcoidosis
Besnier-Boeck disease

Schirmer test
an eye test that measures the quantity of tear fluid produced in 5 minutes; see chaper 12

scintigram
an investigation to measure the function of an organ through the uptake and elimination of a radioactive tracer substance

scleroderma
an autoimmune disease in which the skin becomes tighter; lung, kidney and intestinal disorders may also occur; see systemic sclerosis and CREST syndrome

second degree relative
grandparent, aunt / uncle or grandchild

sensitivity
a term used in relation to a specific test to show how many (part or percentage) of the people with a specific disease have an abnormal test result (see also specificity)

specificity
a measurement in relation to a specific test to show how many (part or percentage) of the people who do not have a specific disease have a normal test result

STAT
Signal Transducers and Activators of Transcription (see chapter 3)

systemic sclerosis ("scleroderma")
a heterogenous group of diseases in which the skin becomes tighter; lung, kidney and intestinal disorders may also occur; examples are limited (CREST syndrome, morphea) and generalized systemic sclerosis

thymus
an organ in which the T-lymphocytes grow, mature and unsuitable T-lymphocytes are eliminated

thrombocytes
blood platelets

thrombosis
clot in a blood vessel; has many causes and antiphospholipid antibodies are one of them

ulcerative colitis
chronic inflammation of the lining of the large intestine with ulceration

uveitis
inflammation of the uvea (choroid and iris of the eye); if the iris alone is inflamed, it is described as anterior uveitis or iridocyclitis

vasculitis
inflammation of blood vessels; the clinical consequence of vasculitis depends on the type (arteries or venes) and size of the vessels

xerophthalmia
dry eyes

xerostomia
dry mouth