Chapter 4: Sialadenitis

Conditions which are included in this chapter range from infections to immunologically mediated disease and others, such as some lymphoproliferative disorders of unknown pathogenesis. They include the following:

1. Acute suppurative sialadenitis
2. Chronic non-specific sialadenitis and sialolithiasis
3. Recurrent parotitis
4. Viral and other infections
   - mumps
   - cytomegalovirus
   - other viruses and microorganisms
5. Postoperative sialadenitis
6. Granulomatous sialadenitis
7. Sjögren's syndrome (autoimmune sialadenitis)
8. HIV-associated sialadenitis
9. Radiation sialadenitis and squamous metaplasia
10. Giant lymph-node hyperplasia
11. Necrotizing sialometaplasia
12. 'Fibrosing sialadenitis' (sclerosing adenocarcinoma)
Acute Suppurative (Bacterial) Sialadenitis

A variety of factors affect the susceptibility of the different salivary glands to bacterial infection but among the most important are their rates of salivary flow, the composition of their saliva and variations in or damage to their duct systems. The most obvious examples are acute suppurative parotitis which is frequently secondary to xerostomia but, by contrast, chronic obstructive sialadenitis and sialolithiasis of the submandibular and other glands can affect otherwise healthy persons. Nevertheless, deterioration of host defences inevitably renders the salivary glands susceptible to haematogenous infections.

Acute suppurative parotitis

Suppurative parotitis was a common postoperative complication particularly of abdominal surgery. Causative factors frequently included dehydration and reduced salivary flow, oral sepsis, exposure to nosocomial infections or septicaemia.

Currently, the single most important predisposing factor for suppurative parotitis, particularly in ambulant patients, is failure of salivary flow. The latter is frequently the result of Sjögren's syndrome or sometimes radiation damage but has also been reported as a complication of tricyclic antidepressive or phenothiazine treatment. These drugs are amongst the most potent antimuscarinic drugs in common, long-term use. In infancy in particular, dehydration due to gastroenteritis may be an important contributory factor.

Decreased salivary flow contributes in two ways to parotid infection. First, drying of the mouth affects the oral microflora and for example, promotes proliferation of such pathogens as *Staphylococcus aureus*, which is otherwise unimportant in oral infections. Second, failure of salivary flow destroys one of the most important mechanisms protecting the gland.

In a comprehensive study of acute bacterial sialadenitis, Raad *et al* (1990) gave details of 29 cases and their predisposing causes, seen between 1970 and 1988, and reviewed reports, between 1911 and 1969, covering 722 patients. Most of the earlier infections had been nosocomial, many had required surgical drainage and the related mortality had ranged from 10% to 50%. Among those who died from this cause, was President Garfield of the United States, after abdominal surgery in 1881. By contrast, during the study period (1970 to 1988) there had been only six nosocomial cases of acute bacterial parotitis and no deaths. In these more recent cases, the most frequently identified predisposing factor was xerostomia due to dehydration (usually secondary to diuretic treatment or other drugs, or hypovolaemia) or Sjögren's syndrome. Surprisingly, in nearly 30% of cases of acute suppurative parotitis, no predisposing cause was noted.

Clinical features

Because of the nature of the underlying diseases, the majority of patients with ascending parotitis are of middle age or older. In the patients reported by Raad *et al* (1990), 83% of cases of acute bacterial parotitis and 76% of acute submandibular sialadenitis were in women and the mean age was 47.5 years.
Typical features are a warm, red, tense, painful and tender swelling of the parotid gland (Fig. 4.1) and, in the more severe cases, fever. The regional lymph nodes may also become swollen and tender.

The parotid papilla is typically red and oedematous, and pus may exude or be milked from the parotid duct. Later, the parotid swelling may become fluctuant and a parotid abscess may form.

The clinical features of acute inflammation, particularly redness of the overlying skin, readily distinguish the onset of infection in those patients whose parotids are already enlarged by the lymphocytic infiltration of uncomplicated Sjögren’s syndrome.

Facial palsy can result from parotitis but is rare. Andrews et al (1989) report three cases and found 10 earlier reports. Such cases merit further investigation to exclude a tumour even when inflammation is obvious.

**Acute submandibular sialadenitis**

Raad et al (1990) have drawn attention to and reviewed reports of this entity of which there were 12 cases among their 29 patients with acute bacterial sialadenitis. Unlike suppurative parotitis, sialolithiasis was an important predisposing factor but xerostomia was also common.

Clinically, acute submandibular sialadenitis differs from parotitis mainly in the site of the swelling and discharge of pus from Wharton's duct.

**Microbiology**

A wide variety of bacteria has been incriminated, but *Staphylococcus aureus* has been the most frequently reported isolate. In both their own and previously reported cases, Raad et al (1990) found that *S. aureus* was by far the most frequent isolate; viridans streptococci were comparatively rare but formed the next most frequent isolate; in one case a Fusobacterium had been found, but in most cases no attempt had been made to isolate anaerobes. However, they noted previously reported anaerobic or Gram-negative aerobic infections, such as by *Pseudomonas aeruginosa*, many of which had been nosocomial. Some of these infections had also been in infants. With current techniques for isolation of anaerobes, it is probable that in view of their numbers in the mouth, they would be more frequently isolated.

**Microscopy**

The earliest changes are vasodilatation and increasing numbers of neutrophils in the parotid vessels, emigrating into the parenchyma and filling ducts. Colonies of bacteria may also be seen particularly in the ducts. As the infection progresses, the ducts become dilated and filled with neutrophils; duct epithelium and then acini are progressively destroyed, leading to formation of microabscesses. If neglected or if host defences are impaired, destruction of the parenchyma progresses and fusion of microabscesses leads to gross abscess formation and destruction of large areas of the gland (Fig. 4.2). Healing is by fibrosis.
Complications

In the past, particularly, complications could include formation of, and discharge of, a parotid abscess through the skin, auditory canal or into the parapharyngeal space, or wider spread of the infection. However, osteomyelitis of facial bones or septicaemia are unlikely to be seen now.

Diagnosis

Though it may be to state the obvious, the first essential is to avoid sialography. The diagnosis should be made on clinical grounds and on the bacteriological findings. A specimen of pus should be obtained, if there is no active discharge, by milking the parotid duct. Pus from the parotid duct is diagnostic of bacterial parotitis and is one of the clinical features distinguishing it from mumps.

Treatment

In view of the predominance of staphylococcal infections, treatment is usually started with flucloxacillin as soon as a specimen of pus has been obtained. Metronidazole may be added to deal with anaerobes but the regimen should be changed if the bacteriological findings and antibiotic sensitivities dictate. Fluid intake should be maintained and salivation encouraged with sialogogues. All cases reported by Raad et al (1990) responded to such treatment and surgery had been unnecessary.

Drainage becomes necessary only if there is gross abscess formation as shown by fluctuation, or the infection fails to subside with adequate antibiotic treatment. If an external incision is unavoidable, it should be made along the line of the related branch of the facial nerve to minimise the risk of damage.

Sialadenitis and Sialolithias

Chronic sialadenitis

Chronic sialadenitis is a common finding in the minor oral glands but can also affect the submandibular or less often, the parotid glands. Duct obstruction is probably a major contributory cause in most cases, especially in the submandibular glands. Bacteriological investigation usually yields viridans streptococci and other oral commensals.

If there is no major calculus formation, the condition is frequently asymptomatic and an incidental finding in minor oral glands on microscopy.

Microscopy

The main features are varying degrees of loss of acini, duct dilatation and a scattered chronic inflammatory cellular infiltrate, usually predominantly lymphocytic (Figs 4.3 and 4.4). Extensive interstitial fibrosis develops and there may be squamous metaplasia of the duct epithelium. Calculus formation may be seen in the dilated ducts.
Chronic sclerosing sialadenitis (Küttner tumour)

This rare disorder affects the submandibular gland and is tumour-like only in the sense that it gives rise to a hard swelling. It appears to be the fibrotic end stage of chronic sialadenitis.

Microscopy

Initially, there is mild duct dilatation with a periductal lymphocytic infiltration, which becomes progressively more widespread and accompanied by periductal fibrosis. Fibrosis is predominantly centrilobular and associated with acinar atrophy (Fig. 4.5).

The duct cells undergo hyperplasia and squamous and mucous metaplasia. There is some extravasation of mucus but the gland finally presents a picture of dilated ducts with striking periductal sclerosis in a sea of lymphocytes. Rarely a sclerosing duct carcinoma can mimic end-stage sclerosing sialadenitis (see Chapter 7).

Excision of the mass and microscopic examination leads to the diagnosis and is curative.

Cystic fibrosis

Cystic fibrosis, a life-threatening disease, is transmitted as an autosomal recessive trait. Most exocrine mucus-secreting glands are affected by production of an abnormal mucus that obstructs ducts and causes progressive damage to the related parenchyma. Parotid gland saliva seems to be little affected but submandibular saliva shows considerable changes (Mandel et al, 1967). Tandler (1987) has reported on the ultrastructural changes in 24 sets of major salivary glands and on lip biopsies in 16 children.

Microscopy

The sublingual glands are most severely affected. In some, the normal architecture is destroyed, but scattered ducts containing dense material remain in a fibrotic stroma. In the most severely affected glands, mucous plugs cause obstruction and chronic inflammation. The dense luminal material appears to be a site of predilection for hydroxyapatite crystallization and formation of sialoliths.

From a clinical viewpoint, salivary gland disorders seem to be negligible in comparison with the other, severe disabilities from which these children suffer.

Sialolithiasis

In an analysis of 1200 reports, Rauch (1959) confirmed that over 80% of calculi formed in the submandibular gland, about 10% in the parotid and 7% in the sublingual glands. Calculus formation in minor glands is also common but usually asymptomatic.
The risk of calculus formation in the submandibular glands is greatest because of the high mucus content and viscosity of its secretion. In addition, the vulnerability of Wharton's duct in the floor of the mouth, and its length may be contributory.

**Clinical features**

The characteristic symptom is pain at mealtimes when the surge of salivary secretion is dammed up behind the obstruction (Fig. 4.6). Alternatively, the obstruction leads to infection and painful swelling of the gland. In yet other cases, there are no symptoms until the stone moves forward along the duct to become palpable in the mouth (Fig. 4.7). Alternatively, it may be seen by chance on a routine radiograph (Fig. 4.8).

Radiography often confirms the presence of calculi but about 40% of parotid and 20% of submandibular calculi are radiolucent. Sialography can be used to locate the latter, but is difficult in the case of the submandibular and sublingual glands; it also carries with it the risk of pushing the stone back into the gland.

Multiple small calculi with chronic inflammation and fibrosis can give rise to a firm, sometimes slightly painful mass, that can mimic a tumour clinically.

**Microscopy**

Salivary calculi appear to form by progressive deposition around an organic nidus which can sometimes be seen by chance in ducts in submandibular gland tissue or in minor salivary glands on microscopy (Figs 4.9 and 4.10). More frequently, small calculi can be seen in various stages of formation either as fusing calcospherites or larger masses with a laminar or sometimes a radial pattern. In many cases, the adjacent duct lining undergoes squamous metaplasia and there is a chronic inflammatory cellular infiltrate in the stroma. Varying degrees of acinar loss may be seen.

**Treatment**

Salivary gland calculi should be treated if large enough to cause obstructive symptoms or if they have led to painful sialadenitis.

In the case of those large enough to be seen or felt, the main principles of treatment are, if possible, to milk the stone forward to the orifice of the duct and to manipulate it into the mouth. More frequently, the stone has to be coaxed as far forward as possible along the duct, which has then to be incised longitudinally, to release the stone. A temporary suture behind the stone is necessary to prevent it from slipping further back. After removal of the stone, the duct should be kept patent by suturing the margins of the incision to the adjacent mucosa. These procedures are discussed in more detail in Chapter 9.

Impacted parotid calculi are typically staghorn in shape and lodge at the site of the two main tributaries of the parotid duct. Intraoral ductotomy and removal of the stone is sometimes successful.
Where there are multiple small stones and widespread chronic inflammation and fibrosis, the gland has to be excised. This is also necessary for stones which are within the gland near the origin of the excretory duct of the submandibular gland and cannot be brought sufficiently far forward for adequate access. For this purpose an external approach is usually easier but because of the danger of damaging branches of the facial nerve should usually be avoided. An intraoral approach should therefore be adopted.

**Recurrent Parotitis**

This disorder is of unknown aetiology and though thought to be infective, this is unproven. Either children or adults can be affected and the main clinical features are recurrent, tender swellings of one or both parotid glands. The interval between attacks may be six months or more and individual attacks typically last for days to weeks.

In children, the disease has usually been reported to resolve spontaneously at or near puberty but this was not confirmed by Maynard (1965) in whose series of 73 patients, all but seven were over 15 years old. The main abnormality found in this detailed investigation was significantly reduced salivary flow rates in symptomatic patients, of 0.041 g/min (resting) and 0.56 g/min (stimulated), compared with 0.082 g/min and 1.29 g/min, respectively, in controls. In those who had spontaneously recovered, the flow rates increased by approximately 50%. Maynard (1965) therefore postulated that the reduced salivary flow rate allowed retrograde infection to become established. Nevertheless, culture of saliva (obtained by cannulation of the parotids to avoid contamination) was positive in only 15 of 75 symptomatic patients compared with 7 of 22 controls.

Takeda (1982) has described tubuloreticular structures about 15-25 nm in diameter in the perinuclear cytoplasm of endothelial cells. Akaboshi et al (1983) have shown a unique pattern of Epstein-Barr virus (EBV) antibodies in children with recurrent parotitis and a considerably higher frequency of EBV antibody carriage than in controls. The main abnormalities in most patients with recurrent parotitis were high titres of antibodies to EBV viral capsid antigen and to EBV-associated nuclear antigen. Antibodies to the early R or D complex or both, also rose in 18 of 34 patients. These abnormal antibody patterns persisted for periods of 3-14 months.

Raad et al (1990), after a review of the literature, concluded that major factors in the pathogenesis were duct dilatation with or without evidence of obstruction and low-grade persistent infection.

**Microscopy**

Donath and Gundlach (1979) and Steinbach and Strohm (1982) have reported mild dilatation of ducts which contained inspissated mucus and desquamated epithelial cells but without significant inflammation in the early stages. There was also periductal oedema and swelling of acinar cells. In the later stages, there was periductal inflammation and increasing but patchy destruction of the lobular structure. There was also conspicuous fibrosis, increased dilatation of the proximal ducts and degeneration of the duct epithelium. Ultimately, some lobules consisted only of proliferated ducts and fibro-fatty tissue. The duct epithelium frequently showed mitotic activity and was also likely to undergo metaplastic change.
The general picture suggests that obstruction, probably secondary to reduced or abnormal secretion, is a major factor in the aetiology of this disease.

Treatment and prognosis

Despite the lack of evidence of an infective cause, antibiotics appear to shorten the duration of attacks and are the usual first line of treatment. In children they are repeated as necessary until there is spontaneous resolution. For adults with persistent disease, a great variety of treatments ranging from duct ligation to low-dose irradiation have been proposed. If there is radiographic evidence of widespread and advanced parenchymal destruction, there is little likelihood of spontaneous resolution. Before fibrosis advances even further and increases the surgical morbidity, the majority of adults with persistent attacks should therefore be advised to have total conservative parotidectomy.

Viral Sialadenitis

Mumps

Mumps is caused by the mumps virus (a paramyxovirus) which can affect many glands other than the parotids, and also neural tissue. The infection is probably droplet spread and the incubation period is typically 18-21 days. In the UK, mumps is now a notifiable disease but with widespread use of immunization it should be a declining disease.

Clinical features

Mumps mainly affects children and after a prodromal period of malaise and anorexia, there is characteristically swelling of one or both parotid glands and fever. The parotid swelling is tense and painful and the submandibular glands may sometimes also be affected.

Microscopy

Microscopically, there is interstitial inflammation of salivary tissue with infiltration by lymphocytes and plasma cells (Fig. 4.11). There is vacuolation and destruction of acinar cells and small haemorrhages. However, destruction of acini is probably less than appears microscopically as there is full functional recovery of the glands.

The diagnosis is usually apparent in typical cases in children and especially when there has been an outbreak of the disease, but mumps may not be suspected when an older adult develops it.

Mumps can be distinguished from other forms of acute parotitis, by the clinical features and absence of a neutrophil leukocytosis, and the diagnosis can, if necessary, be confirmed serologically. The usual choice is by enzyme-linked immunoadsorbent assay (ELISA). Complement fixation is used for quantification of the antibody responses to the S and V antigenic components. Antibodies to the S antigen often reach a peak within a week of the onset of symptoms. Their identification can provide early confirmation of the diagnosis as they rapidly decline and cannot usually be detected after 6-12 months. Complement-fixing antibodies to the V component, by contrast, reach a peak after 2-3 weeks, then slowly decline.
but persist at low levels for years. Specimens taken 2-3 weeks apart showing a fourfold or greater increase in the titre of antibodies is confirmatory. However, if only a late specimen is available, a titre of antibodies to the S antigen greater than that to the V antigen, or antibodies to mumps-specific IgM confirm the diagnosis. Immunofluorescent methods can be used to identify the IgG and IgM antibodies. Past mumps infection is indicated by mumps-specific IgG, or complement-fixing antibodies to the V antigen, indicate immunity to mumps and can be used to exclude it as a cause of parotitis.

The virus can be picked up on swabs of saliva, particularly from near the parotid papilla and can be identified by immunofluorescence.

**Prognosis and treatment**

There is no specific treatment but in children, mumps is usually a mild, self-limiting disease. In adults, mumps is less common, but frequently then causes a more severe illness with such effects as high fever or involvement of other glands and prolonged malaise. After puberty, 20% of males with mumps develop orchitis, but sterility rarely results. Other possibilities include oophoritis or pancreatitis. In children or adults, complications include aseptic meningitis (which is usually self-limiting), encephalitis and permanent unilateral sensorineural deafness. Deafness is the most serious complication in absolute terms but though rare, mumps encephalitis has a significant mortality, particularly in adults.

In the absence of specific treatment, vaccination against mumps is important for children over one-year-old to avoid the risk of deafness. In the UK, the recommended preparation is measles, mumps and rubella triple vaccine which is over 95% effective.

**Cytomegalovirus infection**

This infection was originally called 'salivary gland inclusion' disease from the observation of the conspicuous viral inclusion bodies seen in the salivary glands of 10-30% of stillbirths.

**Clinical features**

The effects of cytomegalovirus on salivary tissue, in itself, appears to be of no clinical significance. The importance of this infection is as a cause of stillbirths or congenital defects, and of potentially lethal disease in immunocompromised patients, particularly among those with the acquired immune deficiency syndrome (AIDS).

**Microscopy**

Congenital cytomegalovirus infection produces in salivary glands distension of duct cells forming giant epithelial cells which contain the typical owl-eye inclusion bodies, which are larger than normal duct cells (Fig. 4.12).
Other causes of infective sialadenitis

Parotitis has occasionally been reported as a feature of infectious mononucleosis, influenza and coxsackie virus infection.

A variety of salivary gland lesions have been described in patients with HIV infection but it is unclear to what extent they are direct effect of this virus. These lesions may cause xerostomia or have histological features in common with Sjögren's syndrome and are described later in this chapter (see p. 49).

A case has also been reported of acute swelling of all the major and minor salivary glands associated with mycoplasmal pneumonia by Wray et al (1980). Though the pneumonia and major gland swellings resolved rapidly with erythromycin treatment, the minor glands remained swollen for two months.

Biopsy of labial glands showed a prominent periductal lymphocytic infiltrate, damage to the ductal epithelium, acinar disruption and mucus spillage into the stroma.

Acute Postoperative Sialadenitis ('Surgical Mumps')

The causes of non-infective postoperative sialadenitis are obscure and Seifert et al (1986) note that it can develop even during intensive antibacterial chemotherapy. They suggest that postoperative sialadenitis may have a pathogenesis similar to that of acute pancreatitis with autodigestion by proteolytic enzymes. However, it is difficult to accept such ideas with the suggestions of treatment by radiotherapy and ganglion blockade, without further evidence of their value.

The peculiar features of postoperative non-suppurative sialadenitis are its immediate onset and spontaneous resolution within 24 hours or less. It seems unlikely that many of these reactions are inflammatory.

Acute transient postanaesthetic sialadenopathy has been described by Rubin and Cozzi (1986) who reviewed earlier reports. In their five cases, bilateral, firm parotid or submandibular gland swellings developed immediately but resolved spontaneously within 24 hours. In one patient, the swelling was associated with airways obstruction which required reinserterion of the endotracheal tube until the swelling subsided. Drugs given pre- and perioperatively did not appear to have been responsible but in all patients there had been straining on the endotracheal tube during anaesthesia. Subsequent laryngoscopy showed only oedema of soft palate and posterior and lateral pharyngeal walls.

Orser (1990) has also reported acute postanaesthetic parotitis in a 74-year-old man who experienced sudden facial pain, trismus and a dry mouth 15 minutes after a general anaesthetic. The left parotid gland was swollen, firm and tender, there were signs of mild dehydration but no fever. The only therapeutic intervention was rehydration and the symptoms resolved after 6 hours.
Management

If acute salivary gland swelling follows anaesthesia, particularly when there has been straining on the tube, the main considerations are to ensure that the airway is clear, to keep the patient under observation for 24 hours and to give rehydration if appropriate. If the swelling has not then subsided, other possible causes such as infection have to be investigated.

Granulomatous Sialadenitis

When granulomas are seen in a salivary gland, the following causes may have to be considered:

--> Tuberculosis and non-tuberculous mycobacterioses

--> Cat-scratch disease

--> Syphilis

--> Deep mycoses

--> Sarcoidosis

--> Wegener's granulomatosis

--> Infarcted Warthin's tumours

--> Foreign-body reactions

--> Calculous or carcinomatous duct obstruction

--> Granulomatous disease of minor salivary glands (Melkersson-Rosenthal's syndrome, cheilitis granulomatosa and glandularis).

In a survey of 57 granulomatous lesions found in 469 major salivary glands, Van der Walt and Leake (1987) found that the most common identifiable cause was calculous duct obstruction (34 cases, all submandibular) and carcinomatous obstruction in five more. Tuberculosis accounted for nine cases, sarcoidosis for two, while in five cases the cause could not be determined.

In the case of obstructive reactions, the granulomas had formed in response to extravasation of mucus and were small, multiple and discrete.

Among other granulomas seen in salivary glands, the most important are probably infarcted Warthin's tumours (in that they are readily treated), tuberculosis (the diagnosis of which can be relatively readily confirmed), and possibly increasingly, non-tuberculous mycobacterioses or deep mycoses, such as histoplasmosis, in patients with AIDS.
Tuberculous and non-tuberculous ('atypical') mycobacterial parotitis

Tuberculosis is an uncommon cause of sialadenitis. Nevertheless, O'Connell et al (1993) reported six cases and Hunter and Thomas (1993) reported five cases seen in the UK, but most of these patients were Asian immigrants. With the rising incidence of mycobacterioses, cases may be seen even more frequently. The parotid glands are usually affected and the infection may involve the intraglandular lymph nodes, or the gland parenchyma.

*Mycobacterium tuberculosis* is the typical cause of tuberculous sialadenitis but increasingly now the non-tuberculous mycobacterioses must be considered, particularly in immunocompromised patients such as those with AIDS.

Clinical features

Tuberculous parotitis typically gives rise to a tumour-like swelling of the gland. Computerized tomography scanning may not clarify the diagnosis but in the case shown in Fig. 4.13, it was highly suggestive. Aspiration cytology may show no more than lymphocytes but may show mycobacteria (Fig. 4.14). If the patient is not already known to have tuberculosis or another mycobacteriosis, the diagnosis is in most cases, made by microscopy after excision of the gland.

Microscopy

The typical features are granuloma formation with Langhans giant cells and caseation, either within lymphoid tissue or in the parenchyma with varying degrees of destruction (Fig. 4.15). Acid-fast bacilli should be detectable with Ziehl-Neelsen or auramine/rhodamine fluorescent staining. If, as is likely, the infection is not suspected preoperatively and no cultures are taken, it may not be possible to distinguish between tuberculosis and a non-tuberculous mycobacteriosis. The latter may be suspected if other organs are involved and particularly if the patient has HIV infection or is otherwise immunodeficient. Confirmation of the diagnosis is by culture if fresh material is available but is slow. More rapid is identification of the bacterium by DNA hybridization which also provides speciation. Mufarrij et al (1982) have described, in such a patient, the appearances produce by *M. avium-intracellulare* in cervical lymph nodes. In this patient, the lymphoid tissue had been replaced by multiple granulomas formed by pink, vacuolated histiocytes which, on Ziehl-Neelsen staining, could be seen to be packed with acid-fast bacilli. Typical epithelioid and giant cells, and caseation were not seen. The granulomas were frequently surrounded or replaced by strands of dense hyalinized material but surrounding lymphocytes appeared unremarkable. Similar changes were seen in the bone marrow and it seems likely that these features were the result of defective cell-mediated immunity rather than the type of infecting mycobacterium. It seems, therefore, that if appearances such as these are seen in salivary glands or related lymphoid tissue, immunodeficiency (possibly due to HIV infection) and an atypical mycobacteriosis, should be considered.
Treatment

Frequently the diagnosis is not made until after excision of the gland which in any case is appropriate treatment. A course of isoniazid or in the case of a non-tuberculous mycobacteriosis, an appropriate multi-drug regimen, should be given.

Cat-scratch disease

Cat-scratch disease is common in the USA but seen occasionally in the UK. The cause is *Bartonella henselae* which does not take up routine stains but has been visualized both at the site of inoculation and in the lesions with a silver stain such as Warthin-Starry.

Children are mainly affected and typically, the infection follows a scratch by a cat, though the history may be uninformative. A small papule or pustule forms at the site of inoculation and leads to lymphadenitis, frequently of the cervical nodes, and this is usually the main manifestation. There is often mild pyrexia and encephalopathy, occasionally conjunctivitis or cranial nerve palsies, but in most cases the infection is mild and self-limiting.

The parotid glands may be swollen in 3% of cases and in an example reported by Premachandra and Milton (1990), in a nine-year-old boy there was also facial palsy. In this case aspiration, biopsy and computerized tomography scanning of the parotid mass were uninformative; a superficial parotidectomy was therefore carried out.

Microscopy

The disease primarily affects intra- or juxtaglandular lymph nodes. The typical features are epithelioid granulomas, frequently with central suppuration and surrounded by a mixed but predominantly mononuclear inflammatory infiltrate (Fig. 4.16). Multiple microabscesses may form in the granulomas and coalesce to form a large abscess. After drainage of any pus, healing is by fibrosis.

Diagnosis depends on the history, the characteristic but not diagnostic histological changes and a positive Rose Hanger skin test. It may also be possible to demonstrate the bacterium by Warthin-Starry staining in the inflamed tissue.

Behaviour and management

When a salivary gland swelling is due to cat-scratch disease, the risks of parotid gland biopsy may prevent a diagnosis being made until the gland is excised. Otherwise, all that is required is drainage of any major abscess by aspiration. Cat-scratch disease of lymph nodes is frequently self-limiting but also responds to antimicrobial treatment such as with cotrimoxazole which may prevent abscess formation.

In the case of the parotid mass due to cat-scratch disease reported by Premachandra and Milton (1990), the facial weakness had not resolved nine months later though the child had otherwise recovered.
Syphilis

Syphilitic parotitis is a recognized entity. It is now largely of historical interest in many countries, but may have to be considered in those where the disease is more prevalent.

Syphilis can involve salivary glands in the early or, more frequently in the later stages, but was rare in the UK, even in the pre-antibiotic era.

Tertiary syphilitic parotitis is characterized by gumma formation, destruction of glandular tissue and fibrous scarring. However, the histological features may not be distinctive and diagnosis is likely to depend on the serological findings.

Deep mycoses

Mycotic infection of salivary glands is likely to be seen only in immunodeficient patients particularly those with HIV infection, when the infection is frequently widespread. Typical features are a tumour-like swelling and granuloma formation, sometimes with central necrosis or caseation. Sometimes the diagnosis can be made on seeing characteristic fungal forms such as the yeast forms of histoplasmosis or cryptococcosis with their characteristic clear haloes. As a generalization, fungi may be seen within epithelioid cells or free in the tissues and are more likely to be seen in the absence of granuloma formation. In the case of histoplasmosis, for example, when there is no granuloma formation, the tissues may be teeming with yeasts, readily visible even with haematoxylin and eosin staining. However, diagnosis may not be possible on microscopy alone but a deep mycosis should be seriously considered if the patient has HIV infection or comes from an endemic area. Other causes of granuloma formation should be excluded and diagnosis should be confirmed if possible by obtaining fresh material for culture.

Treatment is antifungal drugs such as amphotericin (particularly in its liposomal formulation) or with ketoconazole, or one of its analogues, according to the sensitivity of the organism.

Sarcoidosis

This multisystem disease is an important cause of granuloma formation in, and has a predilection for, salivary tissue. Rarely, salivary gland swelling is the first sign (Fig. 4.17). The main and most common sites of tissue injury are the lungs (which are involved in approximately 90% of cases at some stage) and lymph nodes. The skin is affected in about 25% of cases; erythema nodosum is particularly common in acute sarcoidosis but lupus pernio is the most characteristic cutaneous lesion. Ocular damage, particularly uveitis, develops in a similar proportion of cases and can occasionally lead to blindness. Involvement of other organs such as the spleen, bone marrow, liver, kidneys, nervous system (of which facial nerve involvement is the most common effect), musculoskeletal system or heart is well recognized but clinically apparent in only a small minority of cases.
Associated abnormalities include anergy to tuberculin but otherwise normal or, at the site of lesions, enhanced cellular immune reactivity as well as non-specific hypergammaglobulinaemia. There is interference with vitamin D metabolism and hypercalcaemia in some cases and serum angiotensin converting enzyme levels are raised, particularly in acute stages of the disease, in a variable proportion of cases.

Clinical features

The onset is usually between the ages of 20 and 40 years, and can be acute or insidious. The most characteristic manifestation is dyspnoea or cough. This is associated with hilar lymphadenopathy and interstitial pulmonary involvement leading to fibrosis. Asymptomatic cases are frequently detected by radiographic evidence of such changes in routine chest films. In acute cases, there may also be fever, malaise and loss of weight.

Parotid gland involvement is well recognized and swelling of the gland is seen in about 10% of cases. The most severe type of parotid involvement is in Heerfordt's (Heerfordt-Waldenström) syndrome which comprises parotid swelling, anterior uveitis, facial palsy and fever. Xerostomia may result. Another, rare variant is gross bilateral involvement of the parotid and submandibular glands giving a frog-face appearance and is one of the causes of Mikulicz syndrome (see p. 28). However, salivary tissue is involved microscopically, in a high proportion of cases. This can readily be demonstrated by biopsy of minor labial salivary glands.

Microscopy

The changes in salivary glands largely mirror those in other organs and consist of granuloma formation, varying degrees of parenchymal destruction and subsequent fibrosis (Figs 4.18 and 4.19).

The granulomas of sarcoidosis are associated with locally increased T-helper lymphocyte activity. They are non-caseating and characteristically form compact, rounded collections of epithelioid cells with variable numbers of Langhans-type giant cells. Many such granulomas are sometimes clustered together and may be surrounded by dense accumulations of lymphocytes. In ≥ 50% of cases, the giant cells contain laminated concretions (Schaumann bodies) consisting of calcified protein (Fig. 4.20), or stellate inclusions (asteroid bodies). However, neither of these features is pathognomonic.

Direct involvement of the facial nerve in its course through the parotid gland is the probable cause of facial palsy but this is usually temporary. Ultimately the granulomas heal by fibrosis.

Diagnosis

Diagnosis of sarcoidosis can be difficult as there is no single pathognomonic feature and no test is reliably confirmatory. The Kveim test (a tuberculin-like response to a sterile extract of sarcoid-involved human spleen or lymph nodes) causes a papular reaction in 65-80% of patients. Other abnormalities such as raised angiotensin-converting enzyme levels as mentioned earlier may also be helpful but ultimately the diagnosis may have to be made on
the combined clinical and radiographic findings and laboratory tests. Histological confirmation of granuloma formation is mandatory.

If the chest film shows changes compatible with sarcoidosis, demonstration of granuloma formation is frequently possible, without endoscopy, by biopsy of labial salivary glands. The latter is very simply carried out under local anaesthesia, using a 1-cm incision into any part of the inner aspect of the lower lip, but preferably where there is any small palpable mass. If the incision extends to about 5 mm into the lip, it is virtually impossible to fail to obtain a minor gland, the small lobules of which should be visible in the specimen, with the naked eye. The incision should be sutured and, if done competently, there should be no more than brief soreness of the lip for a short period afterwards.

Labial gland biopsy is reported to be confirmatory for sarcoidosis in association with pulmonary or other systemic signs suggestive of the disease in a high proportion of cases, and since it is so simple this procedure should be tried first. It may be more likely to give a positive result than a blind bronchial biopsy and avoid the need for this more hazardous, invasive procedure.

Prognosis and treatment

As a broad generalization, acute cases are likely to be self-limiting while those of insidious onset are more likely to leave permanent tissue damage. Spontaneous resolution can be expected in about 50% of cases.

The main line of treatment for those with significant respiratory impairment, hypercalcaemia, uveitis or other serious complications, is with corticosteroids, particularly prednisolone, usually in a course of about six weeks.

Wegener's granulomatosis

The initial manifestations of Wegener's granulomatosis are typically in the nasopharynx or sometimes the mouth. Salivary gland involvement appears to be uncommon, but examination of the literature suggests that it is less rare than might be expected. Murty et al (1990) could find reports of only three cases but presented two new ones. Another case had been reported by Kavanaugh and Huston (1988) where parotid swelling was the initial manifestation. Patients with salivary gland involvement as a prominent or incidental finding have been described in varying degrees of detail by other workers.

One of the patients reported by Murty et al was a 23-year-old man who had otitis externa, a foul-smelling discharge, trismus, palatal ulceration, and later, a submandibular gland swelling. The latter showed the typical microscopic features of Wegener's granulomatosis. The other, a 55-year-old woman, had a month's history of painless swelling near the angle of the jaw and persistent nasal obstruction with ulceration of the nasal floor on the same side. The swelling in the tail of the parotid gland showed inflammation with multinucleate giant cells and vasculitis typical of Wegener's granulomatosis was present in a nasal biopsy. In both cases, immunosuppressive treatment appears to have prevented spread of the disease to the lungs or kidneys.
Specks et al (1991) reported five cases of salivary gland swelling as a prominent feature of Wegener's granulomatosis in patients ranging from 24-75 years of age. In three of these cases, the submandibular glands, and in the other two the parotid glands were involved. All four of those tested for antineutrophil cytoplasmic autoantibodies showed titres between 1:16 and 1:256. All patients had the limited form of the disease and remission was achieved with prednisone in combination with cyclophosphamide or co-trimoxazole, or both.

Schmidt et al (1989), writing from a referral centre for Wegener's granulomatosis, were prompted by the presentation of a man with this disease and xerophthalmia to look into the frequency of sicca syndrome in 24 of their patients. The diagnosis of Wegener's granulomatosis had been made in these patients by biopsy and the presence of antineutrophil cytoplasmic autoantibodies. Seven of these patients had abnormally low tear production and five other patients complained of recurrent conjunctivitis. Six of the 24 patients had SS-A/SS-B autoantibodies but no comment was made about salivary gland function.

Earlier, Andrassy et al (1983) had noted the presence of SS-A/SS-B autoantibodies in some patients with Wegener's granulomatosis and since they are a relatively sensitive marker for Sjögren's syndrome, it may be that these diseases are associated more frequently than has been hitherto suspected.

Microscopy

The salient features are numerous giant cells, vasculitis and sometimes granulomas. However, in any individual biopsy, one or other of these features may be lacking. The giant cells are often compact with relatively few darkly staining nuclei and eosinophilic or may resemble Langhans' cells. The giant cells may be grouped near blood vessels, be few or numerous in different areas, or associated with a mixed inflammatory infiltrate and granulation tissue in which eosinophils are frequently prominent. Eosinophils may sometimes also be seen in the walls of inflamed vessels but arteritis does not appear to be dependent on their presence.

Necrotizing arteritis is the essential feature in the pathogenesis of Wegener's granulomatosis. Sometimes arteritis may be obscured by the sea of inflammatory cells. Silver stains are therefore useful to make obvious the remnants of the elastica. The arteritis in itself, may be difficult to distinguish from other types of vasculitis such as Churg-Strauss syndrome. The association with giant cells or the clinical features may therefore be necessary to confirm the diagnosis if characteristic pulmonary or renal lesions have not already developed.

Well-formed granulomas rarely seem to have been prominent in the reported cases, except that of Specks et al (1991). Only very ill-defined granulomas have been seen in our material (Fig. 4.21) while Devaney et al (1990) in their analysis of 126 biopsies of the head and neck area, specifically mention that granulomas were found in a minority and they were poorly formed granulomas. Nevertheless, the current American Society of Rheumatology criteria for the classification of Wegener's granulomatosis (Leavitt et al, 1990) includes granulomatous inflammation as the main histological criterion, and it was noted in biopsies on 71 of 85 patients with the disease.
**Diagnosis**

Leavitt et al (1990) found that diagnosis had a sensitivity of 88% and a sensitivity of 92% if only two of the traditional criteria (urinary sediment with red-cell casts or more than five red cells per high-power field; nodules, cavities or fixed infiltrates on chest radiographs; oral ulcers or nasal discharge; and granulomatous inflammation on biopsy) were present. Haemoptysis increased the sensitivity and specificity of the diagnosis even further.

Devaney et al (1990) regard the diagnosis of Wegener's granulomatosis as definitive only if all the recognized histological features are present in a biopsy as well as involvement of the lungs, kidneys and head and neck sites. However, with such widespread disease the possibility of effective treatment is likely to be small. Early diagnosis is occasionally possible as a result of salivary gland biopsy. This may enable treatment to prevent lethal pulmonary or renal involvement. Salivary gland biopsy also causes less morbidity than lung biopsy.

The diagnosis may therefore be made on the histological findings together with clinical or other evidence of oronasal, pulmonary or renal involvement. If the histological findings in a patient with a salivary gland swelling leave the diagnosis uncertain, biopsy of any nasal or oral lesions is readily carried out and likely to be helpful. A chest radiograph and urine examination are also essential for confirming the diagnosis or the extent of the disease. A significant titre of antineutrophil cytoplasmic antibodies may contribute to confirmation of the diagnosis.

**Treatment**

If the disease is localized to salivary glands or the nasopharyngeal region or both, early cytotoxic treatment with, for example, cyclophosphamide or azathioprine may be life-saving. Such treatment has serious toxic effects, such as an increased risk of lymphoreticular neoplasms, and should not therefore be given unless the diagnosis is reliably based on such criteria as those mentioned earlier.

However, the hazards of cytotoxic treatment have to be balanced against the life-threatening nature of the disease and should not be unduly delayed until the disease is so far advanced that all doubts about the diagnosis are finally removed.

**Infarcted Warthin's tumours**

Granuloma formation was seen in 6% of 232 Warthin's tumours in our material, apparently as a result of infarction. In most such cases, the bulk of the tumour has been destroyed and the granulomas may be mistaken for tuberculosis or sarcoidosis. It is discussed more fully in Chapter 6.

**Foreign-body reactions**

Foreign-body reactions in salivary glands may be provoked by exogenous material such as escape of radiocounter material into the parenchyma, or by endogenous material such as crystalloids, calculi or extravasation of tumour products, particularly mucin from a mucoepidermoid carcinoma or sebum from a sebaceous adenoma or carcinoma. In all such
cases, the cause of the foreign-body reaction should be apparent from the appearances of the rest of the gland. By contrast, granuloma formation in Warthin's tumours as mentioned earlier is typically associated with destruction of most of the tumour.

**Duct obstruction**

As mentioned earlier, Van der Walt and Leake (1987) found that the single most common identifiable cause of a granulomatous reaction in salivary glands was calculous duct obstruction. In many fewer cases the obstruction was due to a carcinoma. In either case the cause should be apparent.

**Granulomatous diseases of minor salivary glands**

**Granulomatous cheilitis**

Swelling, usually of the lower lip is sometimes the result of granulomatous inflammation of unknown cause, but is occasionally a manifestation of the Melkersson-Rosenthal syndrome, which comprises:

--> Recurrent facial palsy

--> Facial swelling, but particularly of the upper lip

--> Fissured tongue.

In some cases, the lip swelling is lymphoedematous and granulomas are not seen.

Granulomatous inflammation and swelling of the lip or lips alone is sometimes called Miescher's syndrome.

**Crohn's disease**

Granulomas may be found in the lips, but labial salivary tissue is probably involved only by extension of inflammation in the adjacent tissue rather than being primarily affected.

**Cheilitis glandularis**

Cheilitis glandularis is a rare disorder particularly of adult males, in whom the lower lip becomes swollen and firm but in the most severe cases can be penetrated by fistulous tracts. The cause is unknown but smoking and exposure to hot sunshine and wind, and possibly genetic factors may be contributory.

Clinically, in addition to swelling of the lip, the labial salivary glands may become nodular with inflamed and swollen orifices. The simple type, characterized by small painless orificial lesions with dilated canals, can progress to superficial or deep suppuration. In the last case, deep abscesses, fistulous tracts and scarring may result.
The main microscopic features appear to be glandular hyperplasia, duct dilatation, sometimes with oncocytosis, and long-standing bacterial infection (Fig. 4.22).

Weir and Johnson (1971) state that 18-35% of reported cases have subsequently developed squamous carcinomas of the lip, but this may be the result of environmental factors and, in particular, chronic exposure to strong sunshine.

**Sjögren's Syndrome**

Sjögren's syndrome, as originally described in 1933, comprises the combination of dry mouth and dry eyes. Sjögren later noticed the association with rheumatoid arthritis and it is noteworthy that Sjögren's syndrome is one of the few conditions which can develop in any of the connective-tissue diseases and is therefore a criterion for inclusion of a disease in this group. However Sjögren's syndrome, despite multiple autoantibodies, may also be unassociated with any other connective-tissue disease. In addition, Sjögren-like syndromes can be associated with other immunological disorders such as AIDS or graft-versus-host disease, as discussed later (p. 55), where a similar autoimmune component may not be demonstrable.

Traditionally, the term 'Sjögren's syndrome' is used to describe the combination of dry eyes and dry mouth due to destruction of glandular tissue. Rheumatoid arthritis or, less frequently, another connective-tissue disorder is associated. This combination of diseases is now termed secondary 'Sjögren's syndrome'. Primary Sjögren's syndrome by contrast, comprises dry mouth and eyes without other associated connective-tissue disease. It has been given adequate consideration only in relatively recent years, and this has probably increased the difficulties of surgeons in assessing benign lymphoepithelial lesion as discussed later (p. 179).

Major differences by which primary Sjögren's syndrome differs from secondary is that it is characterized by:

--> More severe xerostomia and xerophthalmia

--> More widespread dysfunction of other exocrine glands and consequent complications

--> More frequently complicated by lymphoma or other lymphoproliferative diseases

--> A different autoantibody profile.

Unfortunately, primary Sjögren's syndrome is sometimes still referred to by its early name 'sicca syndrome' and the term 'sicca complex' is sometimes used indifferently for either variant of Sjögren's syndrome or for dry mouth or dry eyes due to other causes, unrelated to the connective-tissue diseases, such as sarcoidosis, thalassaemia or amyloidosis (Chapter 3).

More recently, the picture has been complicated further by HIV-associated sialadenitis where there may be xerostomia and the histological changes of so-called benign lymphoepithelial lesion or Sjögren's syndrome but lacking autoantibodies typical of the latter.
Although autoantibody formation is characteristic of Sjögren's syndrome, no single autoantibody test is consistently positive and the commonly used screening tests available in many hospitals may prove inconclusive. Many of these autoantibodies can sometimes also be found particularly in the elderly without Sjögren's syndrome or even in the absence of any form of autoimmune disease. However, SS-B may be found in approximately 55-75% of patients with primary Sjögren's syndrome, the majority of whom lack rheumatoid factors, while in secondary Sjögren's syndrome, in addition to signs of a connective-tissue disease, rheumatoid factor is positive in approximately 75% and SS-A antibodies are present in 50-80% of patients.

Clinical features

Women are frequently affected in the ratio of 9-10:1 and are usually 50-60 years old. There is another smaller peak of incidence at the age of approximately 30 years.

Despite progressive loss of salivary or lacrimal secretion or both, it must be emphasized that patients are surprisingly unpredictable in their complaints and though parotid flow rates, for example, can be shown objectively to be reduced, dryness of the mouth may not be mentioned or, apparently, even noticed. However, there may be complaints of complications such as abnormal taste sensation or of the infections resulting from reduced salivary flow as discussed earlier.

Complete xerostomia causes the mucosa to become parchment-like (Fig. 4.22) but partially reduced salivary flow is not readily apparent on inspection and the oral mucous membranes usually appear moist. However, there may be absence of the normal pooling of saliva in the floor of the mouth and there may be sticky froth in the folds of the mucosa. The dorsum of the tongue typically becomes lobulated and frequently, the oral mucosa is red and sore as a result of infection by Candida albicans secondary to the reduced salivary flow (Fig. 4.24). Angular stomatitis can also result from the same infection (Figs 4.25 and 4.26).

In some cases, the onset is relatively acute and occasionally there can be painful bilateral parotid swelling (Fig. 4.27). In many cases, however, no swelling may develop or be noticed.

Drying of the conjunctiva can cause an unpleasant gritty sensation and there may be secondary conjunctivitis, but early keratconjunctivitis sicca is frequently asymptomatic.

In secondary Sjögren's syndrome, the associated connective-tissue disease, usually rheumatoid arthritis, is likely also to be apparent.

Microscopy

The essential features are progressive lymphocytic infiltration of salivary tissue, acinar destruction but some preservation and proliferation of duct epithelium to form so-called epimyoepithelial islands. The lymphocytic infiltration is initially periductal, and unlike non-specific sialadenitis is typically not associated with significant duct dilatation (Figs 4.28 and 4.29). The lobular boundaries are preserved and there is neither invasion nor destruction of tissue other than glandular parenchyma. In the lymphocytic infiltrate as well as in the
peripheral blood, CD4 lymphocytes predominate (Itescu et al, 1989).

Early changes of Sjögren's syndrome can be seen in minor (labial) gland biopsies, though epimyoepithelial islands are not usually found in these glands. It is also important in these glands to distinguish the lymphocytic infiltrate of Sjögren's syndrome with that of non-specific sialadenitis. By contrast, in major glands which have been removed because of a painful, tumour-like swelling, the changes are far advanced and little or no glandular tissue may remain.

The changes are the same as those of so-called 'benign lymphoepithelial lesion' (Chapter 8) where, as a result of progress of the lymphoplasmacytic infiltrate to produce a swelling, total or near-total replacement of acinar tissue is also typically seen (Fig. 4.30).

Whether or not Sjögren's syndrome and benign lymphoepithelial lesion are distinct entities remains controversial, but a high proportion of the latter may be found to have clinical and autoantibody abnormalities consistent with Sjögren's syndrome on further examination (Ostberg, 1983).

Very rarely, major cystic change in the lymphoepithelial lesion of Sjögren's syndrome may be seen. Hong et al (1990) describe a woman of 60 years with xerostomia of three years' duration, an autoantibody profile typical of Sjögren's syndrome, but nodules predominantly of CD4 lymphoproliferation, lining two large (2 cm) cysts in the parotid gland. These workers could only find a single earlier report of such changes and speculated whether the changes Sjögren's syndrome had developed in the walls of a pre-existing lymphoepithelial (branchial) cyst. However, they drew no comparisons with the HIV-associated parotid cysts described below.

**Diagnosis**

The association of rheumatoid arthritis and dry mouth (without any other cause) in a woman of middle age or older is virtually pathognomonic of Sjögren's syndrome. However, there is no single diagnostic test which will reliably confirm the diagnosis.

Investigations to confirm the diagnosis of Sjögren's syndrome may include the following:

1. Sialography. This may show punctate sialectasis in the case of Sjögren's syndrome (Fig. 4.31), or alternatively, may outline a neoplasm.

2. Labial salivary gland biopsy. Changes in minor labial salivary glands (Figs 4.32 and 4.33) closely correlate with those in the parotid glands but must be carefully assessed as discussed below (Fig. 4.34).

3. Objective measurement of the salivary flow rate (Chapter 5) and, if reduced, to exclude other causes, particularly drugs.

4. Assessment of tear secretion (Schirmer test) or, better, slit-lamp examination of the conjunctiva and cornea.
5. Autoantibody studies, particularly for rheumatoid factor, antinuclear antibodies and if possible SS antibodies.

6. Haematological examination. A raised erythrocyte sedimentation rate and anaemia in the absence of any other cause are suggestive of rheumatoid disease.

Though not a routine investigation, MRI is sometimes informative (Figs 4.24 and 4.25). In assessing labial gland biopsies, nonspecific sialadenitis must be excluded. This is characterized by scattered, rather than periductal infiltrates, variable numbers of neutrophils, acinar damage, interstitial fibrosis and duct dilatation.

It is also important to assess several labial salivary gland lobules, as the greater the number of lymphocytic foci, the closer the correlation with Sjögren's syndrome. If there are more than five foci per 4 mm², the accuracy of diagnosis is 95%.

Even in the absence of any clinical features suggestive of autoimmune disease, autoantibody studies should preferably be carried out. Typical autoantibody findings are listed in Table 4.1. Antisalivary duct antibody is present but its titre does not correlate with the severity of the disease. Hypergammaglobulinaemia and raised levels of acute-phase proteins and a raised erythrocyte sedimentation rate are associated in those with active connective-tissue disease. There is a strong association with HLA DR3 in the case of primary Sjögren's syndrome and with HLA DR4 in secondary Sjögren's syndrome.

Table 4.1 Typical patterns of autoantibodies in primary and secondary Sjögren's syndromes

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary duct antibody</td>
<td>10-36%</td>
<td>67-70%</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>± 50%</td>
<td>± 90%</td>
</tr>
<tr>
<td>SS-A antibodies</td>
<td>5-10%</td>
<td>50-80%</td>
</tr>
<tr>
<td>SS-B antibodies</td>
<td>50-75%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>± 5%</td>
<td>± 75%</td>
</tr>
</tbody>
</table>

However, the inconstant association between these various abnormalities is suggested by a detailed study of 113 patients with clinical signs of primary Sjögren's syndrome by Saito et al (1991). They found periductal lymphocytic infiltrates consistent with Sjögren's syndrome in labial salivary gland biopsies in 67 patients. Periductal lymphocytic infiltrates had a significant correlation with the presence of rheumatoid factor, SS-A and SS-B autoantibodies and keratoconjunctivitis sicca, but not with stimulated salivary flow rates. Many patients without labial gland biopsy changes indicative of Sjögren's syndrome therefore had as greatly
diminished salivary flow rates as those that did.

It is important to have slit-lamp examination to exclude early, asymptomatic keratoconjunctivitis sicca. If present, it can be treated early before there is any corneal damage.

**Treatment**

Administration of artificial tears is essential to prevent corneal damage and delay the progress of keratoconjunctivitis sicca, otherwise treatment is largely palliative to relieve dry mouth (Chapter 5) and any infective complications.

Immunosuppressive therapy with corticosteroids, cyclophosphamide or azathioprine has been tried in an effort to control the immunological abnormalities in Sjögren's syndrome, but has not been shown to be effective as salivary gland destruction is usually too far advanced. Moreover, such treatment is likely to increase the risk of malignant change. Fox et al (1988) have reported that treatment with hydroxychloroquine decreases autoantibody production, including SS-B, and other indices of autoimmunity, and suggest that such treatment by modulating lymphoproliferation may reduce the risk of neoplastic change. Hydroxychloroquine did not improve salivary or lacrimal secretion, but it may be that in these patients also, glandular destruction was too far advanced.

Rarely, otherwise uncontrollable parotid pain and swelling may necessitate parotidectomy. Apart from the possible morbidity of this operation, the removal of this diseased and non-functional salivary tissue is no loss to the patient and may lessen the risk of malignant change. By contrast, the risk of malignant change is likely to be raised by radiotherapy which should therefore be avoided.

**Complications**

These fall into the following categories:

1. Those resulting from the drying particularly of mucosal surfaces (Table 4.2).

2. Those relating to any associated autoimmune diseases (Table 4.3).

3. Lymphoreticular diseases, particularly lymphomas (Table 4.4).

The prevalence of Sjögren's syndrome depends both on the incidence of the underlying disease and the frequency with which Sjögren's syndrome is associated. Thus rheumatoid arthritis affects approximately 2% of the general population and approximately 15% of such patients develop Sjögren's syndrome. Systemic lupus erythematosus is considerably less prevalent but Sjögren's syndrome is associated in approximately 30%. Primary biliary cirrhosis is relatively rare but Sjögren's syndrome is present in at least 70% of cases. Some of these diseases such as tubulointerstitial nephritis or primary biliary cirrhosis can be asymptomatic when the patient is first seen.
Table 4.2 Sjögren's syndrome. Complications of exocrine gland dysfunction.

<table>
<thead>
<tr>
<th>Area</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Keratoconjunctivitis sicca; progressive ocular damage</td>
</tr>
<tr>
<td>Mouth</td>
<td>Dryness; suppurative parotitis; candidiasis; dental infections</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Dryness of the mucosa; nasal crusting; otitis media; chronic bronchitis; recurrent pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Dysphagia; postcricoid webbing; pancreatitis</td>
</tr>
<tr>
<td>Other mucocutaneous surfaces</td>
<td>Xeroderma; vaginal dryness.</td>
</tr>
</tbody>
</table>

Sjögren's syndrome has a significant but infrequent association with organ-specific autoimmune diseases, particularly thyroiditis.

Table 4.3 Sjögren's syndrome associated diseases

- Lupus erythematosus
- Progressive systemic sclerosis
- Mixed connective-tissue disease
- Polymyositis/dermatomyositis
- Raynaud's phenomenon
- Primary biliary cirrhosis
- Vasculitis
- Central nervous system disease*
- Tubulo-interstitial nephritis
  - renal tubular acidosis
  - hypokalaemic periodic paralysis
- Lymphocytic interstitial pneumonitis
- Primary pulmonary hypertension
- Thyroiditis
- Pernicious anaemia
- Pemphigus vulgaris
- Myasthenia gravis
- Antiphospholipid syndrome

* Secondary to vasculitis or antiphospholipid syndrome.
Lymphoma and other lymphoreticular complications

The main neoplastic complication of Sjögren's syndrome is development of lymphoma. Connective-tissue diseases, in general, but in particular rheumatoid arthritis, are associated with an increased incidence of lymphomas which are mostly extrasalivary. Lymphomatous change in benign lymphoepithelial lesion is also well recognized as discussed in Chapter 8 and there appears to be a strong association between Sjögren's syndrome and monocytoid B-cell (MALT) lymphoma (see p. 186).

Table 4.4 Lymphoreticular complications of Sjögren's syndrome.

| B-cell lymphomas (typically MALT lymphomas, possibly of monocytoid type) |
| T-cell lymphomas rarely |
| Monoclonal gammopathy |
| Multiple myeloma |
| Waldenström macroglobulinaemia |
| Franklin's heavy-chain disease |
| Aplastic anaemia. |

Clinical features suggestive of lymphomatous change are persistent or late onset of rapid salivary gland swelling, lymphadenopathy or loss of weight. Immunological changes reported to be associated with lymphomatous change or related lymphoreticular disease include:

--> Falling immunoglobulin (particularly IgM) levels

--> Falling titre of rheumatoid factor

--> Rising \( \beta_2 \)-microglobulin titre

--> Rising serum macroglobulin titre

--> Appearance of monoclonal light chains in serum or urine.

Other lymphoreticular complications listed in Table 4.4 are rare.

HIV-Associated Sialadenitis and Sicca Complex

Chronic parotitis in children is said by Prose (1990) to be virtually pathognomonic of HIV infection. In adults, a sicca syndrome and lymphocytic infiltration of salivary glands are also well-recognized abnormalities.

One of the earliest reports was by Gordon et al (1984). Ulirsch and Jaffe (1987) described the microscopic changes in detail, including formation of epimyoeipithelial islands, compatible with Sjögren's syndrome in three patients. HIV antibodies were present in two and suspected in the third. One of these patients also complained of dry eyes and arthralgias; another had a polyclonal hypergammaglobulinaemia.
In five patients with generalized lymphadenopathy syndrome together with dry mouth and eyes or swollen salivary glands, Couderc et al (1987) found intense lymphoplasmacytic infiltration of salivary glands in labial biopsies. However, as described by Berman et al (1988) in 100 cases of HIV infection, antinuclear, SS-A or SS-B antibodies or rheumatoid factor were detected in none of them, including one whose disease most closely resembled rheumatoid arthritis. Labrouyie et al (1993) have detected HIV-1 replication particularly in germinal centres in these lesions which, they concluded, had probably been primarily induced by the virus. Labrouyie et al (1993) also found that both their lesions were monoclonal.

An autoantibody picture compatible with Sjögren's syndrome does not, therefore, appear to be associated with the sicca syndrome of HIV infection, but rarely a patient with connective tissue disease may acquire HIV infection. De Clerck et al (1988) reported a female patient with dry mouth and eyes together with symptoms of systemic lupus erythematosus, including the presence of antinuclear antibodies and also HIV infection. Labial gland biopsies showed lymphoplasmatic infiltration. Another exceptional case is the patient reported by Calebresse et al (1989), namely, a 64-year-old woman with seropositive rheumatoid arthritis who developed Sjögren's syndrome and persistent lymphadenopathy but remission of the articular disease followed shortly after a brief febrile illness. The last seems likely to have been due to exposure to HIV infection from her husband who in turn had acquired it from a blood transfusion. Minor salivary gland biopsy showed changes consistent with Sjögren's syndrome but, unlike typical cases, there was a predominance of CD8 lymphocytes. Clearly, dual pathology of this sort is most unusual but illustrates the complexities of the possible interactions of different diseases affecting the immune system.

AIDS-associated lymphadenopathy or lymphomas presenting as salivary gland lesions have also been reported by Ioachim et al (1988).

Parotid cysts associated with HIV infection

From a total of 15 lymphoepithelial lesions, Smith et al (1988) have reported 12 typical examples in parotid gland resections specimens from 11 males at high risk from AIDS (Figs 4.5 and 4.6). Microcysts lined by squamous or cuboidal epithelium were present in all cases and adjacent salivary tissue showed periductal and interstitial lymphocytic infiltrates (Fig. 4.37 and 4.38). All 11 patients had generalized lymphadenopathy concurrent with painless parotid swellings, which had developed over periods of one to four years, but none reported dryness of the mouth or eyes.

Microscopic examination of the parotid glands showed typical features of benign lymphoepithelial lesion with epimyoepithelial islands. In 9 of the 12 specimens, follicles in the lymphoid infiltrate were numerous, large, irregular in shape and contained many tingible body macrophages. In 6 of these 9 specimens, the follicles showed changes suggestive of the abnormalities associated with HIV infection. Mantle-zone lymphocytes were absent from the periphery of the follicles whilst in others, mantle-zone lymphocytes penetrated into the centres of the follicles - processes termed by Burns et al (1985), 'mantle-zone effacement' and 'follicle lysis'.

27
The interfollicular lymphoid tissue contained prominent small blood vessels which were frequently thick-walled, and varying numbers of scattered immunoblasts and plasma cells (Fig. 4.39). In some cases, there were also lymphoid cells with clear vacuolated cytoplasm (monocytoid B cells) or multinucleated cells resembling Warthin-Finkeldey giant cells.

In a more detailed study of 12 HIV-positive patients with sicca syndrome, Itescu et al (1990) describe what they termed 'diffuse lymphocytosis syndrome', with CD8 lymphocytosis and widespread visceral lymphocytic infiltration, particularly dense in the salivary glands and lungs. All had bilateral parotid swellings which were massive in nine patients. Minor salivary gland changes typical of Sjögren's syndrome were found in all eight specimens taken, but though all patients had polyclonal hypergammaglobulinaemia, only five were positive for rheumatoid or antinuclear factors and none were positive for anti-SS A or B: 11 of these patients were black, 10 of them were HLA DR5 (compared with 13 of 45 matched controls) but only 1 was HLA-DR3.

Among 18 patients at risk from AIDS, Holliday et al (1988) have reported, painless facial swelling due to benign lymphoepithelial parotid cysts. These were bilateral in most cases and visible in computerized tomography scans. Microscopy showed the cysts to be lined by cuboidal and squamous epithelium overlying nodules of hyperplastic lymphoid tissue. Fibrous capsules and sinusoids partly or completely surrounding the cysts were often identified. Lymphocytic infiltrates, together with germinal follicle formation, were also found along the ducts in the adjacent salivary tissue. Cervical lymphadenopathy due to follicular hyperplasia was associated and 11 of 13 of these patients were HIV-positive.

Other reports of parotid lesions in patients with or at high risk from AIDS, have been by Finfer et al (1988), Colebunders et al (1988) and Som et al (1981). Of the 23 patients reported by Finfer et al (1988), 16 were tested for antinuclear antibody and rheumatoid factor, but all were negative. Only 1 patient complained of dry mouth and eyes but laboratory investigation showed no abnormalities. Fine needle aspiration biopsy showed 'changes consistent with benign lymphoepithelial lesion'.

In brief, therefore, a Sjögren-like syndrome with salivary gland swelling and similar microscopic appearances, can be a feature of HIV infection. However, cyst formation in some cases, helps to differentiate the picture from Sjögren's syndrome. In some cases, dryness of the mouth or eyes seems to have been absent and though autoantibodies may sometimes be detectable in HIV-infected patients, an autoantibody picture typical of Sjögren's syndrome is not found. Other salivary gland lesions associated with HIV infection include parotid swellings due to involvement of intra- or periparotid lymphoid tissues in the lymphoproliferative process of this disease, or a salivary gland lymphoma.

Inevitably, there are exceptions to these generalizations and as mentioned earlier, cystic lympho-proliferative lesions, possibly indistinguishable microscopically from those seen in HIV disease, have rarely been described in patients with otherwise typical Sjögren's syndrome.
Parotid swelling with changes typical of benign lymphoepithelial lesion particularly with cyst formation, in youngish adult males, who may also have xerostomia but absence of autoantibodies typical of Sjögren's syndrome is therefore strongly suggestive of HIV infection. Important distinguishing features are summarized in Table 4.5.

**Table 4.5** Typical differences between Sjögren's syndrome and HIV-associated salivary gland lesions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sjögren's syndrome</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Females:males = 9:1</td>
<td>Predominantly males</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Usually &gt; 50 years</td>
<td>Usually 20-40 years</td>
</tr>
<tr>
<td><strong>Lymphadenopathy</strong></td>
<td>Typically absent</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Xerostomia/xerophthalmia</strong></td>
<td>++</td>
<td>Frequently absent</td>
</tr>
<tr>
<td><strong>Cystic salivary gland lesions</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>RF, ANF, SS-A and SS-B</td>
<td>None characteristic for Sjögren's syndrome</td>
</tr>
<tr>
<td><strong>Lymphatic infiltrate</strong></td>
<td>CD4</td>
<td>CD8</td>
</tr>
<tr>
<td><strong>HLA</strong></td>
<td>DR3/DR4</td>
<td>DR5</td>
</tr>
</tbody>
</table>

**Graft-versus-host disease**

Graft-versus-host disease is most common after bone-marrow transplantation because of the depth of immunosuppression required. A sicca syndrome can result, particularly in the late stages and sequential biopsies of minor salivary glands (Medina *et al*, 1984) have shown early periductal lymphocytic infiltration but, unlike Sjögren's syndrome, the infiltrate is relatively light. There is also lymphocytic infiltration of duct walls and acinar destruction associated with progressive fibrosis.

Labial salivary gland biopsy may therefore be useful in confirming the diagnosis of graft-versus-host disease, particularly the chronic form, and assessing its progress.

Another effect of graft-versus-host disease on minor salivary glands is the formation of small submucosal oral retention cysts (Barrett and Bilous, 1984).
Radiation Sialadenitis

Radiation sialadenitis refers only to the acute reaction which develops within about 24 hours of exposure to therapeutic irradiation of the area. The parotid glands, being composed of serous cells only, are more sensitive to irradiation than other salivary glands and are predominantly affected. They become swollen and tender; there is a sharp rise in salivary amylase levels and diminished salivary flow rate. The reaction is self-limiting and typically resolves within a few days.

When the dose to glands exceeds 50 Gy, the effects of permanent radiation injury become apparent after a period of a few weeks, as more severe and persistent xerostomia.

Microscopy

There is initial swelling and vacuolation of acinar cells followed by necrosis. The small arteries show endothelial swelling followed by endarteritis, thickening of the media and fibrinoid deposition in the lumen which becomes reduced or obliterated.

Salivary tissue has little power of recovery; there is usually permanent destruction of acini and fibrous replacement. Among the fibrous tissue, only small areas of ductal epithelium persist and may undergo metaplasia, and there is usually a scattered lymphocytic cellular infiltrate (Fig. 4.40).

As in Sjögren's syndrome, treatment of dry mouth and its effects is palliative and discussed in Chapter 5.

Radioactive iodine is used for the treatment of thyrotoxicosis or thyroid carcinoma but is taken up by salivary tissue as well as the thyroid gland. Salivary gland function may be impaired as a consequence but has rarely been reported.

Radiation-induced squamous sialometaplasia

Leshin et al (1990) have described extensive squamous metaplasia in salivary tissue after adjunctive radiotherapy to a squamous-cell carcinoma of the cheek. Using Mohs' micrographic surgical technique, they were able to distinguish radiation-induced squamous metaplasia from squamous-cell carcinoma in a recurrence of the tumour.

Microscopy

Leshin et al (1990) have described anastomosing cords and strands of squamous cells with large hyperchromatic nuclei, resembling the original carcinoma cells. However, the lobular architecture of the gland remained intact and the squamous cells were orientated along the long axis of the ducts and focally involved some acini. The acini were atrophic, there was surrounding stromal oedema, scattered inflammatory cells, intralobular fibrosis and mucus plugging of ductules. These latter features are typical of subacute radiation damage but the importance of these findings is the emphasis they give to distinguishing them from recurrent carcinoma and so avoiding overtreatment. The main distinguishing features are that in radiation-induced squamous metaplasia, the lobular architecture and the acini remain intact,
though the acini are inflamed and atrophic. The squamous metaplasia may resemble the original tumour cytologically, but is linear and along the axis of the ducts. Unlike necrotizing sialometaplasia, there is no ischaemic lobular necrosis with mucin pooling.

**Giant (Angiofollicular) Lymph-Node Hyperplasia (Castleman's Disease)**

This condition (Castleman's disease), of unknown aetiology, usually affects the thorax. The cervical lymph nodes are involved in up to 15% of cases but occasionally involve the parotid lymph nodes to produce a tumour-like mass. Variable systemic complaints, particularly with the plasma-cell and multicentric types, may be associated. Involvement of intraparotid lymph nodes has been reported by Cavallaro et al (1985) and Woolgar and Hook (1991). In the later's case, a 24-year-old white woman had had a slowly growing, pre-auricular swelling for a year. No other abnormalities were found and a superficial parotidectomy was carried out. However, histological examination showed angiofollicular lymph-node hyperplasia of the localized hyaline vascular type.

**Microscopy**

In the hyaline vascular type of disease, the nodal architecture is typically replaced by multiple follicles consisting of tight, concentric layers of lymphocytes surrounding hyalinized blood vessels but highly vascular interfollicular tissue. The endothelial cells of the central blood vessels are swollen, often proliferate and are interleaved by hyaline material (Fig. 4.41).

In the case reported by Woolgar and Hook (1991), the mass was intranodal but surrounded by parotid gland parenchyma.

**Behaviour and prognosis**

Angiofollicular lymph node hyperplasia is usually benign and Stansfeld and d'Ardenne (1992) note that it may be present for many years before the mass becomes so large that removal becomes necessary. Nevertheless, occasional cases of lymphomatous change and, more recently, development of aggressive vascular neoplasms, has also been reported in this disorder by Gerald et al (1990). Excision of the mass is, therefore, indicated and is effective. When the parotid gland is affected, this is likely to have been carried out because of the tumour-like appearance and for cosmetic reasons.

**Necrotizing Sialometaplasia**

Necrotizing sialometaplasia is a tumour-like, but self-limiting lesion usually of the palate, first described by Abrams et al (1973). It appears to be far more common in the USA where many more cases (in relation to numbers of salivary gland neoplasms) have been reported.

**Clinical features**

Most patients are over 40 years of age and males are affected in the ratio of 2:1 or 3:1. Many are heavy smokers. The most common appearance is a firm, erythematous swelling of the palate; it causes little or no pain and usually ulcerates. The ulcer, which may be up to
3-cm across, is typically deep, circumscribed, with raised erythematous edges and may resemble a carcinoma.

Microscopy

There is preservation of the lobular boundaries but pseudoepitheliomatous hyperplasia as a result of squamous metaplasia of ducts and acini (Figs 4.42 and 4.43). The latter form compact rounded lobules of squamoid epithelium. These cells have only a small amount of cytoplasm surrounding the nucleus and the lobules may have mucous cells in the centre. Some mitoses may be seen but there is no epithelial atypia. In addition, there is infarction of mucous acini often causing extravasation of mucus, to which there is a prominent inflammatory reaction (Fig. 4.44).

The appearances are readily mistaken, as has happened in the past, for a squamous-cell or mucoepidermoid carcinoma.

Rarely, the same changes have been seen in other minor glands and also in major glands after surgery, when it seems likely that the blood supply has been damaged. Since the hard palate also has a tenuous blood supply and since also lobular infarction is a feature of this lesion, it seems likely that it results from ischaemic necrosis and a reparative reaction.

Behaviour and prognosis

Many of these lesions have been excised, and this may be useful to confirm the diagnosis, but they are usually self-healing, with a time course of 6-10 weeks. Recurrence is virtually unknown.

Sclerosing Adenocarcinoma

Rarely an adenocarcinoma of salivary glands, like sclerosing adenocarcinomas of the breast, as discussed in Chapter 7, can give rise to a picture mimicking chronic sclerosing sialadenitis. In such a case, the ducts are surrounded by dense fibrous tissue, little acinar tissue may remain and the neoplastic nature of the ducts may not be immediately apparent.

Allergic Sialadenitis

A variety of potential allergens such as some drugs (chloramphenicol or tetracycline), pollens and other substances can give rise to acute parotid swelling. When there are peripheral eosinophilia and eosinophils in the saliva, an allergic basis for the reaction appears probable but the immunopathogenesis is unknown. It may also be noted that the drugs mentioned (unlike the penicillins, for example) rarely cause allergic reactions of recognizable types such as IgE-mediated rashes, anaphylaxis or serum sickness.

If the diagnosis can be confirmed, treatment is by avoidance of the triggering agent. Antihistamines are of little value as the reaction is not of the immediate type.
Angiolymphoid hyperplasia with eosinophilia (Kimura's disease)

This is usually associated with raised IgE levels. The disease and particularly, salivary gland involvement, is rare in the West but common in China, Japan and Singapore. Tham et al (1981) for example, reported 14 Chinese patients in whom the parotid or submandibular salivary glands or both were involved. The patients ranged from 14 to 64 years of age (average 39 years), the majority were males and the duration of their disease ranged from 1 month to 15 years. The swellings were firm, rubbery and rarely tender but the overlying skin was coarse and indurated. Lymph nodes were not involved in eight of the patients.

Microscopically, there is progressive replacement of acini by lymphocytes, with follicle formation, and eosinophils. A few ducts persist but become surrounded by thick layers of collagen. Occasionally masses of eosinophils form aggregates with central necrosis; in others, numerous mast cells are scattered among the eosinophils or there are giant cells resembling Warthin-Finkeldey cells. Vascular proliferation is a constant feature. Eosinophilia typically ranges from 0.9-6. x 10⁹/litre.

Though Kimura's disease may have an atopic basis, excision of the lesions reported by Tham et al (1981) was effective and without recurrence in the period of follow-up.

Angiolymphoid hyperplasia without peripheral eosinophilia is more common in the West. It is frequently confused with Kimura's disease but there is considerable evidence that it should be categorized as an epithelioid haemangioma. Unlike Kimura's disease, it is most often dermal and, microscopically, the endothelial cells are plump, eosinophilic and epithelioid in appearance and though eosinophils are numerous in both conditions, lymphoid follicles are less prominent. Epithelioid haemangioma does not appear to have been reported in salivary glands.

Kimura's disease (angiolympoid hyperplasia with eosinophilia) appears to have an atopic basis and can involve the parotid glands.

Notes

1. T. Langhans (1839-1015), German pathologist; also described the cytotrophoblastic layer in the chorionic villi.

2. F. Ziehl (1859-1926), German bacteriologist and physician. F. K. A. Neelsen (1854-1894), German pathologist and inventor of the Ziehl-Neelsen technique.

3. C. E. Heerfordt (born 1871), Danish ophthalmologist.

4. J. C. Waldenström (born 1906), Swedish physician.

5. J. N. Schaumann (1879-1953), Swedish dermatologist who demonstrated that sarcoidosis was a systemic disease.

6. F. Wegener (born 1907), German pathologist.
7. E. Melkersson, Swedish physician. C. Rosenthal, German neurologist.

8. J. F. Miescher (1811-1887), Swiss pathologist.

9. B. B. Crohn (1884-1983), American physician. Modestly, did not attach his name to the disease but, because of the varied manifestations, Francis Avery-Jones proposed at an international conference in 1932 that it should be adopted.

10. H. S. C. Sjögren (born 1899), Swedish ophthalmologist; also developed the technique for corenal transplantation.

11. Apparently the same Warthin who described the tumour. W. Finkeldey, German pathologist.
