RA Cawson et al: Pathology and Surgery of the Salivary Glands

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Chapter 1: Salivary Glands: gross and microscopic anatomy

The three major salivary glands are the paired parotid, submandibular and sublingual. There are also very many minor glands in virtually all parts of the oropharyngeal mucosa with the exception of the dorsum of the tongue.

Development

The epithelium of human salivary glands appears to be derived from ectoderm of the oral cavity or, in the case of von Ebner's glands (which surround the circumvalate papillae) and extraoral (nasopharyngeal) salivary tissue, from ectoderm.

The anlage develops as a solid bud from the oropharyngeal epithelium at about six weeks *in utero* for the parotid glands and seven weeks *in utero* for the submandibular glands. The club-shaped terminal bulb soon undergoes dichotomous branching and a lumen develops, initially in the main branch. At the same time there is condensation of mesenchyme round the terminal bulbs to form a capsule and later the inter- and intralobular septa. The stroma of the parotid glands is rich in lymphocytes which eventually form the intra- and paraparotid lymphoid tissue.

The primitive ducts consist of an inner layer of cuboidal cells and an outer layer of flattened myoepithelial cells (Figs. 1.1 and 1.2). As secretory units differentiate, myoepithelial cells become confined to the acini and distal ductal components. In the parotid glands, the striated ducts cannot be reliably identified until after birth. Functional maturation follows establishment of feeding.

The facial nerve becomes engulfed by embryonic glandular parenchyma between the 16th and 21st week of foetal life.

The Parotid Glands

Each parotid gland is a slender, lobulated, lozenge-shaped structure which has been likened to an inverted pyramid. It has a small superior surface and much larger anteromedial, posteromedial and superficial surfaces. Its anterior border overlies, and is densely adherent to, the posterior part of the masseter muscle. Superiorly, this border is limited by the zygomatic arch, on occasion, reaches as far as the carotid triangle. Its posterior border abuts on to the tragal cartilage superiorly and extends inferiorly to overlap the upper part of the sternomastoid muscle, to which it is only loosely attached. The superior surface is related to the external auditory meatus and the posterior aspect of the temporomandibular joint, whilst its anteromedial surface is attached to the masseter muscle, posterior border of the mandibular ramus and the medial pterygoid muscle. The posteromedial surface is grooved by the posterior belly of the digastric muscle, styloid process and its attached muscles and ligaments. The superficial surface is covered by skin and superficial fascia, which is condensed immediately over the gland to form its capsule. Anteriorly, it is covered by the posterior border of the
platysma muscle.

Within the capsule are the superficial parotid lymph nodes and the greater auricular nerve, which is derived from the cervical plexus and provides sensory innervation to the lower two-thirds of the pinna.

Several structures run through the gland and are of considerable surgical importance. The most notable of these is the facial nerve (see below). The external carotid artery enters the posteromedial surface of the gland before dividing into the maxillary artery and the superficial temporal artery. The latter gives off the transverse facial artery before emerging from the superior surface whilst the maxillary artery leaves the gland from its anteromedial surface.

The retromandibular vein is formed in the gland by the union of the maxillary and superficial temporal veins and leaves its inferior extremity to join the posterior auricular vein and become the external jugular vein. However, the retromandibular vein divides within the gland and its anterior division courses forwards to emerge from the anterior border of the gland as the posterior facial vein. These veins are exceptionally easy to image with ultrasound. They lie immediately deep to the plane of the facial nerve but are of little value in locating the latter.

Within the parotid, the tree-like tributary ducts join near the anterior border of the gland and leave it to pass forward over the superficial surface of the masseter along an imaginary line drawn from the angle of the mouth to the attachment of the earlobe. The duct, Stenson's duct, passes through the buccinator muscle to open into the mouth at the parotid papilla. Small accessory glands may lie along the line of the parotid duct.

### The facial nerve

The branching patterns of the facial nerve are exceedingly complex and hence have been inadequately or inaccurately described in classical anatomical texts. The location and variations of these branches are of immense significance and this fine detail has been derived mainly from surgical research. These details and the anatomical relations of the main trunk of the facial nerve at the stylomastoid foramen are therefore discussed in Chapter 9, in relation to the surgery of the parotid gland.

### The deep and superficial lobes

Much has been written about the superficial and deep lobes of the parotid gland and whether there is an isthmus between them. At first sight, this would appear to be an academic exercise, as it is common surgical knowledge that there is always parotid tissue medial to the facial nerve. The reasons for this controversy are twofold. First, there has been a desire to establish why development of a surgical plane round the facial nerve within the parotid gland is relatively simple. Second, it seems likely that the presence and site of an isthmus determines the origin and management of deep lobe tumours, as discussed in relation to surgery of parotid gland tumours.
The autonomic nerve supply

The secretomotor fibres to the parotid gland emerge from the otic ganglion which is closely related to the auriculotemporal nerve. Preganglionic fibres reach the ganglion from the inferior salivary nucleus via the glossopharyngeal nerve, tympanic plexus and lesser petrosal nerve.

The sympathetic supply reaches the gland from the superior cervical ganglion via the neural plexus surrounding the major blood vessels.

The effects of sympathetic and parasympathetic impulses and of drugs acting on these autonomic pathways are discussed in more detail in Chapter 5.

The parotid lymphoid tissue

There are periparotid nodes, while within the glands there are also many nodes and small, less well organized aggregates of lymphoid tissue.

McKean et al (1985) carried out an autopsy study mainly on elderly persons, on the distribution of these nodes. Using strict anatomical criteria for defining the nodes and excluding small lymphoid aggregates, they found 193 intraparotid nodes in ten cadavers. Virtually all of these nodes were superficial to the facial nerve and only 16 nodes were in the deep lobe. Most of the latter were superficial to the retromandibular vein.

The Submandibular Glands

The submandibular salivary glands consist of a large superficial and a smaller deep lobe which are continuous around the posterior border of the mylohyoid muscle. The medial aspect of the superficial part lies on the inferior surface of the mylohyoid muscle; the lateral surface is covered by the body of the mandible while its inferior surface rests on both bellies of the digastric muscle. Its inferior surface is covered by the platysma muscle, deep fascia and skin. The anterior facial vein runs over the surface of the gland within this fascia and is joined superiorly by the facial artery, which is for the most part related to the deep surface of the gland. Posteriorly, the submandibular and parotid glands are separated by a condensation of deep cervical fascia - the stylohyoid ligament. The deep part of the gland lies on the hyoglossus muscle where it is related superiorly to the lingual nerve and inferiorly to the hypoglossal nerve and lingual vein. The capsule of the gland is well defined and derived from the deep cervical fascia which splits from the greater cornu of the hyoid bone to enclose it.

The submandibular duct (Wharton's duct) is formed by the union of several tributaries and is about 5 cm in length. It emerges from the middle of its deep surface and runs in the space between the hyoglossus and mylohyoid muscles to the anterior part of the floor of the mouth, where it opens onto a papilla to the side of the lingual frenulum. In its anterior part, it is related laterally to the sublingual glands and may receive many of their ducts. During its course on the hyoglossus muscle, it is crossed from its lateral side by the lingual nerve.

The submandibular gland receives its blood supply from branches of the facial and
lingual arteries. Venous drainage accompanies these vessels. There are several lymph nodes immediately adjacent to the superficial part of the gland; these drain the latter as well as adjacent structures.

**The autonomic nerve supply**

The parasympathetic supply to the submandibular gland is from the superior salivary nucleus via the nervus intermedius, facial nerve, chorda tympani, lingual nerve and submandibular ganglion. Multiple parasympathetic secretomotor fibres are distributed from the submandibular ganglion which hands from the lingual nerve.

The sympathetic nerve supply is derived from the superior cervical ganglion via the plexus on the walls of the facial and lingual arteries.

**The Sublingual Glands**

The sublingual salivary glands lie in the anterior part of the floor of the mouth, between the mucous membrane, the mylohyoid muscle and the body of the mandible close to the symphysis, where each may produce a small depression - the sublingual fossa. Each gland has numerous excretory ducts which either open directly onto the mucous membrane or into the terminal part of the submandibular duct.

**The Minor Glands**

Innumerable minor salivary glands are widely distributed in the lateral margins of the tongue, the lips and buccal mucosa, palate, glossopharyngeal area, and retromolar pad. Overall, they contribute about 10% of the saliva. Palatal glands are the sites of predilection for minor gland neoplasms.

**Microscopic Anatomy**

The parenchyma of each major gland is enclosed by a fibrous capsule which also contains some elastic tissue as well as blood vessels, autonomic nerve fibres and IgA-secreting plasma cells. The capsule is well defined in the parotid and submandibular glands, but less well developed in the sublingual and minor glands. The glands are split into lobules of variable size by fibrous septa.

The parenchyma consists of varying proportions of serous and mucous cells and ducts (Figs. 1.3 and 1.4).

The serous acini consist of wedge-shaped secretory cells with basal nuclei surrounding a lumen which forms the origin of an intercalated duct. The cytoplasm of the serous cells is densely packed with heavily basophilic secretory granules ready to discharge their contents, predominantly amylase. At the ultrastructural level, these cells contain densely packed endoplasmic reticulum in addition to the secretory granules and other cytoplasmic organelles (Fig. 1.5).

The mucous acinar cells have almost clear cytoplasm, consisting of vacuoles
containing sialomucins, and have flattened basal nuclei. Ultrastructurally, the mucous cells contain relatively little endoplasmic reticulum. In the case of the mixed glands and in particular the submandibular gland, the mucous cells have caps (demilunes) of basophilic, granular serous cells.

The parotid glands are almost exclusively serous (Figs 1.6 and 1.7), while the submandibular glands are mixed (Fig. 1.8), although the serous component predominates and the mucous component is both variable and sometimes minimal. The sublingual gland is predominantly mucous whilst the minor glands if the tongue, lips and buccal mucosa are seromucinous. The minor glands of the palate, glosopharyngeal area, retromolar pad and lateral borders of the tongue tend to be predominantly mucous (Figs 1.9 and 1.10).

Fat is a conspicuous component of the parotid glands and tends to increase in amount with age (Fig. 1.6).

Myoepithelial cells lie between the basal lamina of the acinar cells and the basal membrane of the acinus (Figs 1.11 and 1.12). Myoepithelial cells vary in their morphology and cannot be reliably identified by light microscopy. When their recognition is important in tumour diagnosis, reliance if frequently placed on immunocytochemistry to confirm that they are strongly S-100 protein and myosin positive but have variable keratin reactions. More recently, it has been shown that S-100 protein has three forms and staining patterns vary according to whether monoclonal or polyclonal antibodies are used and which of the S-100 variants are used. Though many believe that S-100beta is localized to myoepithelial cells and that the alpha-variant frequently stains duct or acinar cells, conflicting findings have been reported by other workers. In particular, Dardick et al (1991), in a careful study of normal salivary glands, have found that normal myoepithelial cells were S-100 negative, but strongly positive for cytokeratin 14 and smooth muscle-specific protein. Only the associated nerve fibres stained to a variable degree for S-100 protein and more reliably, for neurone-specific enolase. These workers showed by electron microscopy that nerve fibres were external to the basal lamina of acini and their surrounding myoepithelial processes but the gap between them was sometimes as little as 300 nm. They therefore concluded that S-100 staining of the network of unmyelinated nerve fibres closely associated with the normal myoepithelium of salivary glands has been misinterpreted as positive staining of myoepithelial cells.

By contrast, neoplastic myoepithelial cells may acquire the ability to stain positively for S-100 protein, but their variability in staining and misinterpretation of the immunohistochemical findings in the past, means that the role of these cells in the histogenesis of certain tumors may perhaps have to be reassessed.

Ultrastructurally, the cytoplasm of myoepithelial cells contains microfilaments of actomyosin, which run parallel to the outer surface (Fig. 1.13), glycogen granules and lipofuscin. Pinocytic vesicles, indicative of active transport of materials between the intra- and extracellular spaces, are also present.

The duct system

The intercalated ducts are short. They are lined by a single layer of cuboidal epithelium with relatively large, central nuclei and are surrounded by myoepithelial cells (Fig.
The intercalated duct cells contain few organelles but actively secrete fluid.

The intercalated ducts are continuous with the striated ducts (Figs. 1.7 and 1.8) which have a brush border (microvilli) on their luminal face and parallel finger-like cytoplasmic extensions from the opposite pole. Ultrastructurally, the parallel infolding of the basal lamina is conspicuous as are the many mitochondria (Fig. 1.15). These cells actively secrete bicarbonate, regulate the water content of saliva and can secrete trace elements and iodine. The duct system also actively secretes or reabsorbs sodium, potassium, chloride and other ions.

The striated ducts run into the interlobular duct system which has a simple transport function. Mucous cells are an occasional finding in striated ducts (Fig. 1.16).

**Sebaceous tissue**

Groups of sebaceous glands are scattered throughout the parotid gland parenchyma and can be seen if sufficient tissue is examined (Fig. 1.17). If a section is cut in the appropriate plane, the sebaceous tissue can be seen to be arising from small ducts.

**Saliva**

**The mucosa-associated lymphoid tissue (MALT)**

The mucosa-associated lymphoid tissue is part of the much larger gut-associated lymphoid tissue (GALT) and like the latter secretes IgA. This salivary mucosa-associated lymphoid tissue can give rise to primary MALT lymphomas especially in lymphoepithelial lesions. Secretory IgA consists of a dimer joined by a secretory piece protein formed by the epithelial cells of the duct system. The relative amounts of IgA secreted by the different salivary glands varies widely. Its apparent function is to form a barrier to the adhesion of bacteria to the oral tissues. However, the mouth teems with bacteria, and dental caries and gingivitis typically progress unchecked unless controlled by artificial preventive measures. IgA deficiency is also one of the most common immunodeficiency disorders, affecting approximately 1 in 600 of the general population, but there is no evidence that deficiency leads to greater susceptibility to oral infections. In some cases at least, IgA deficiency may be compensated by IgG or IgM secretion in significant amounts in the saliva but there appears to be little evidence of any contribution of this change to the prevention of oral infections.

This lymphoid tissue is present in the capsule of the parotid glands and within the substance of these glands. Within the gland, the lymphoid tissue usually has a well-defined capsule and a peripheral sinus, but at the hilum the lymphoid tissue often merges with the gland parenchyma. Conversely, salivary gland tissue can often be found in intra- and paraparotid lymph nodes and also in lymph nodes in the upper cervical chain. In children, it is not uncommon to find both ductal and acinar tissue in this lymphoid tissue but in adults, only ducts are usually found (Fig. 1.18). Many believe that Warthin's tumours and lymphoepithelial cysts originate in this ectopic salivary tissue.
Other antibacterial components of saliva

The function of substances such as lysozyme and lactoferrin secreted by the salivary epithelium and which have antibacterial activity \textit{in vitro} is unclear.

From the clinical viewpoint therefore, the main contribution of saliva to defence against infection appears to be the largely mechanical effect of its flow, washing down microbes into the gastric acid.

Digestive enzymes in saliva

Amylase is the main digestive enzyme secreted in the saliva and it can break down polysaccharides such as starch into sugars. This process is assisted by the comminution and mixing of saliva with food by mastication. Nevertheless, food is normally so briefly in the mouth that this component of digestion is only initiated before swallowing, but later completed in the small intestine by pancreatic amylase.

In acute inflammatory disease of the major salivary glands, particularly mumps, serum levels of the salivary isoenzyme, S-amylase, are raised but estimation of serum S-amylase levels is of no more than theoretical value in the diagnosis of mumps (Chapter 4). S-amylase is also produced by a variety of tissues with the result that serum S-amylase levels are also raised in diverse conditions such as acute alcohol intoxication, diabetic ketoacidosis and the postoperative state.

By contrast, estimation of P-amylase is of value in the early diagnosis of acute pancreatitis and its level is raised within the first day after the onset of symptoms.

Notes

1. V. von Ebner (1842-1925), Austrian histologist.

2. Niels Stenson (1638-1686) gives a particularly strong aura of respectability to salivary gland studies in that he was beatified by Pope John Paul II in 1988. He is now the Blessed Niels Stenson and thereby on the first step leading to canonization and sainthood. Stenson (or Stensen), a Dane, discovered the parotid duct at the age of 22, described other glands in the mouth and gastrointestinal tract, and made several other contributions to anatomy. Contrary to general belief at that time, Stenson maintained that tears had a lubricant function and were formed in the lacrimal glands. Ultimately, Stenson was appointed Apostolic Vicar of the North and gave up his scientific studies. He devoted himself to pastoral duties, living in poverty as an ascetic, and died at the age of 48.

3. T. Wharton (1614-1673), physician to St Thomas's Hospital London, described the submandibular duct in 1656.
Chapter 2: Investigation of salivary gland disease

Many techniques of investigation are research tools and do not, as yet, have an established role in diagnosis. The chief promise of some, such as immunohistochemistry or electron microscopy, is that they may contribute to more precise categorization of difficult tumour types. However, this book is not intended as a comprehensive treatise on salivary gland research. Investigational techniques will therefore be discussed only in relation to the practical problems of diagnosis and management.

Investigation has two main purposes. The first is to establish as precise a diagnosis as possible to guide the clinician towards the optimal mode of treatment. The second, which particularly applies to autoimmune disease, may only be applicable postoperatively but may be helpful in assessing the patient's ultimate prognosis. Benign lymphoepithelial lesion is the main example. The diagnosis is likely to be made only after operation but it is important then to discover whether there is any evidence of autoimmune disease (Chapter 4). The latter in turn may increase the likelihood of development of lymphoma or other complications. In addition, variants of lymphoepithelial lesion may be indicative of HIV infection.

Clinical Investigation

Much depends on the duration of the history and the clinical features of individual lesions. These may make it clear whether or not a tumour is present and if so, may suggest whether it is benign or malignant. The age and sex of the patient, in conjunction with knowledge of the demographic features of salivary gland lesions, should also be taken into account in the process of diagnosis. A history of systemic disease and of drugs being taken should also be carefully assessed. For example, a salivary gland swelling in a woman of 60 years, with a history of rheumatoid arthritis or other connective-tissue disease has a high chance of being due to Sjögren's syndrome. In such a patient, the possibility of lymphoma needs also to be considered. In a male particularly if between the ages of 20 and 40 years, a cystic salivary gland swelling should suggest the possibility of HIV infection.

Rarely, drugs can give rise to salivary gland swellings but more often they are the cause of xerostomia (Chapter 5). The presence of endocrine or metabolic disease may be useful in recognizing sialosis (Chapter 6).

The following are the main investigatory measures available to the clinician or pathologist:

1. Imaging techniques

   Radiography and sialography

   Computerized tomography (CT)
Magnetic resonance imaging (MRI)

Ultrasound

Scintiscanning

2. Histopathology and related methods

Frozen sections

Aspiration cytology

Histochemistry

Immunohistochemistry

Electron microscopy

3. Salivary gland function tests

Flow rates

Sialochemistry

4. Tests for related or contributory systemic disease

Bacteriology

Haematology

Autoantibody studies and other immunological tests.

**Imaging**

Detailed imaging of diseased salivary glands is neither cost-effective nor necessary in all cases. In the majority, a thorough clinical examination yields adequate surgical information to permit safe removal once consent has been obtained. However, for some patients, imaging is necessary to stage their disease and plan surgical treatment. The first group of tests, namely radiography and related techniques, is useful to locate tumours and calculi, or abnormalities such as sialectasis in Sjögren's syndrome. The relative merits of each modality are discussed below. Ultrasound has not as yet been widely applied or become of established value in the investigation of salivary gland disease, but some have found it useful in the assessment of both inflammatory and neoplastic disease. Scintiscanning has also not proved to be of great value in diagnosis, requires bulky and expensive equipment, and is not without some risk to the patient. The methods currently in use are sialography, computerized tomography (CT), nuclear magnetic resonance imaging (MRI) and ultrasound.
Sialography

Sialography remains the most popular method of assessment of ductal inflammatory and degenerative disease despite the more sophisticated imaging techniques currently available (Figure 2.1). Focal or diffuse ductal strictures and ectasia are easily demonstrated and give useful information concerning the probable outcome of conservative management. However, its use is limited by the fact that space-occupying lesions are neither reliably detected nor localized. Sialography should be restricted therefore to cases with recurrent parotid or submandibular swelling in which no discrete mass, other than a calculus, can be palpated (Figs 2.2 and 2.3).

The technique is not difficult, but some expertise is required to cannulate the parotid and submandibular ducts in an atraumatic fashion. The injection of contrast medium occasionally causes some discomfort and it is for this reason alone that sialography is rarely possible, even if indicated, in an unsedated child. Over-filling of the duct system by excessive injection pressure may result in extravasation of contrast medium into the surrounding parenchyma. This produces a brisk local reaction, causing discomfort for several days.

CT Scanning and MRI

There are clear indications for CT or MRI which can be summarized as follows:

**Major glands**

1. Masses confined to the deep lobe of the parotid gland (Figs 2.4 and 2.5).
2. Tumours with involvement of both the deep and superficial lobes of the parotid gland (dumb-bell tumours).
3. Parotid tumours presenting with facial weakness, other neural deficit or indication of malignancy (Figs 2.6 and 2.7).
5. Submandibular gland tumours with neural deficit or fixation to the mandible.
6. Recurrent disease (Figs 2.8 and 2.9).

**Minor glands**

1. Tumours of the palate with suspected involvement of the nose or maxillary antra (Figs 2.10 and 2.11).
2. Any tumour with clinically ill-defined margins.

Several studies have assessed the reliability of both CT and MRI in the detection of malignant salivary disease. Neither is, nor can be expected to be, completely reliable, though reasonable specificity rates are claimed for both. However, it is not for this purpose that
imaging is generally required but rather for detecting suspected lesions within the salivary glands and providing surgically useful images of the extent of disease (Figs 2.12 and 2.13). Sensitivity rates approaching 100% are claimed for both modalities and image quality is influenced mainly by the generation of scanner or image protocol adopted.

The majority of tumours within the major glands examined by CT give higher attenuation values than surrounding normal glandular tissue (Figs. 2.14 and 2.15). The resolution of soft-tissue attenuation in thin slices achieved by modern generation scanners is exceptional, improved by intravenous contrast and is perfectly adequate for the examination of salivary glands. There is no longer the need for CT sialography, which was advocated at a time when scanning resolution was considerably inferior. Unfortunately, disruptive artefacts may be introduced by extensive dental restorations which can significantly detract from the image quality.

Occasionally, CT scanning will show calcifications in a salivary gland tumour and this strongly suggests that it is a pleomorphic adenoma. They are unlikely to be seen in conventional radiographs.

MRI has proven to be equally sensitive in the detection of salivary neoplasms (Fig. 2.9). Within the major glands they give low signal intensity with $T_1$-weighted protocols and relatively high signal intensity with $T_2$ and balanced protocols. Although both $T_1$ and $T_2$ images show the margins of the lesion with equal clarity, the tumour composition is better defined with $T_2$ sequences and the detection of subtle areas of disease by short inversion of tau inversion recovery (STIR) sequences (Figs 2.8 and 2.9). The introduction of paramagnetic contrast materials has improved this aspect of MRI further, but increased the expense.

Both CT and MRI have proved useful in demonstrating cystic AIDS-related lymphoepithelial lesions (Fig. 2.17).

Unlike CT, the quality of MRI is not influenced by the state of the patient's dentition. Occasionally also, MRI will indicate whether a parapharyngeal tumour has originated in the parotid gland or from minor pharyngeal glands, but this distinction can rarely be reliably demonstrated.

In clinical terms therefore, there is essentially little to choose between CT and MRI for the diagnosis of salivary gland disease: the ultimate decision will therefore be mainly influenced by the local availability of scanners, cost and personal preference.

**Ultrasound**

The most attractive feature of ultrasound is that most hospitals have access to suitable equipment and expertise in its use for the assessment of less accessible structures, for example heart valves and the foetus. It is relatively simple to obtain good, diagnostic quality scans of the major salivary glands as they are, to a large extent, subcutaneous structures and there is the additional advantage that the technique is non-invasive. Several studies have shown that the parenchyma of the glands can be depicted in detail and, in expert hands, an accurate picture of the duct system can be obtained. Small tumours can be detected and, it is suggested, a degree of suspicion about their malignant potential aroused (Figs 2.18 to 2.20).
The retromandibular vein is reliably seen and its relationship to a tumour mass gives some information about possible involvement of the facial nerve.

Despite these attractions, ultrasound has yet to become established as a useful clinical investigation for salivary disease. The reasons are, first, that the images do not provide sufficient operative information for the surgeon and, second, there are areas of the salivary glands that may be obscured by bone from ultrasonic assessment.

**Histopathology and Related Techniques**

Histopathology is generally understood to apply to microscopy of paraffin-blocked sections. The most commonly employed and most generally useful stain is haematoxylin and eosin. Though the picture is two-dimensional and largely artefactual, histopathology remains the most reliable diagnostic method because of the existence of a vast body of knowledge of the microscopic appearances of an enormous variety of diseases. In particular, of course, salivary gland tumours and other lesions have been categorized in terms of their histopathology. The latter allows extensive examination of many areas of a large specimen such as a parotid tumour and may therefore reveal localized malignant change which may be missed in frozen sections or fine-needle aspiration. Block specimens and mounted sections also provide a permanent record for retrospective evaluation when necessary.

The great disadvantage of conventional histopathology of course, is that it provides only a postoperative diagnosis. However, this is still valuable in confirming or contradicting the choice and extent of surgery and the later stages of postoperative management. As discussed below, fine-needle aspiration biopsy or frozen sections can be used for pre- or intraoperative diagnosis, but their accuracy is less than, and must always be checked against, conventional histopathologic examination of the specimen afterwards.

The histopathology of salivary gland tumours is, nevertheless, a difficult area and indeed a major purpose of this atlas is to try to help pathologists who do not have extensive experience in this field. However, the fact remains that the categorization of a few salivary gland tumours is still a subject of some doubt.

**Histochemistry**

Histochemistry has limited applications in salivary gland tumour diagnosis. The demonstration of minute amounts of intracellular mucin may, however, be useful in distinguishing poorly differentiated mucoepidermoid from squamous-cell carcinomas, which are likely to have a worse prognosis. Histochemistry is also valuable in the preliminary investigation of neuroendocrine tumours by use of silver (Grimelius) and other stains. Silver staining may also be useful in demonstrating the reticulin pattern in some lymphomas. Other suggests uses of histochemistry are confirmation of the nature of oncocytic cells by use of phosphotungstic acid haematoxylin (PTAH) and the identification of crystalline and other inclusions.
Immunohistochemistry

Immunohistochemistry, though sometimes invaluable, has many more limitations than were earlier anticipated. The chief difficulties include the sharing of markers by cells of different origin and the loss of markers as a result of neoplastic change. However, immunohistochemistry is valuable for differentiating difficult tumours such as dysplastic or anaplastic carcinomas from lymphomas or sarcomas, for distinguishing non-neoplastic lymphoproliferative lesions from lymphomas and for differentiating B- and T-cell lymphomas. Another use for immunohistochemistry is in the identification of the rare neuroendocrine tumours. Their small cells are positive for epithelial markers such as epithelial membrane antigen but negative for common leukocyte antigen. They are typically chromogranin and neurone-specific enolase-positive. Specific hormones or their precursors can be identified, if required and the facilities are available. Rarely also, a paraganglioma may appear in the parotid region and be mistaken for a salivary gland tumour such as an acinic cell carcinoma with many clear cells. Paragangliomas stain in a generally similar manner to neuroendocrine cells but are negative for epithelial markers.

Rarely, an adenocarcinoma of a salivary gland may mimic a thyroid tumour but can be readily recognized by its failure to stain for thyroglobulin.

Another use for immunohistochemistry is in the identification of amelanotic melanomas which are typically neurone-specific enolase, S-100 protein- and vimentin-positive, but negative for epithelial membrane antigen.

Spindle cell tumours (myoepitheliomas) of salivary glands may occasionally be difficult to differentiate from connective-tissue tumours. Myoepitheliomas are usually recognizable by the presence of obviously epithelial components of the tumour, but if these are lacking, the myoepithelial cells should be identifiable by their staining with both epithelial markers and vimentin, and actin or myosin. This is unlike most other spindle cell tumours which are positive for vimentin but not epithelial markers. An exception is the exceedingly rare synovial sarcoma which can appear in the parotid region, and may be positive for both of these markers. The apparent staining of myoepithelial cells for S-100 protein has been discussed earlier (see Chapter 1). Immunohistochemistry has the great advantage over electron microscopy that it can frequently give an answer more quickly and be carried out in a histopathology laboratory without bulky and expensive equipment. It can also be applied to frozen sections for intraoperative diagnosis. Indeed some markers can only be used on frozen sections as the relevant epitopes are destroyed by conventional specimen processing.

Though there are many immunohistochemical studies on the cell populations of salivary gland tumours and though a case has been made for differentiation of low-grade polymorphous adenocarcinomas from adenoid cystic carcinomas by immunohistochemistry (see Chapter 7), it cannot be said that this method is as yet of proven usefulness in the microscopic diagnosis of the more difficult salivary gland tumours, apart from those already mentioned.
Frozen Sections

Surprisingly, Gnepp (1988) states that the first use of frozen sections was in Holland in 1818. It was not until the introduction of the cryostat over 130 years later, and improvements in technique that frozen sections became a valuable and widely accepted ancillary diagnostic measure. By consultation between pathologist and surgeon during the operation, frozen sections should provide answers to three important questions which bear directly on management, namely:

1. Is the lesion benign or malignant?
2. If malignant, is the tumour high or low grade?
3. Are the margins of excision tumour-free?

Unfortunately, Gnepp (1988) in his extensive review of the literature, has confirmed that of all sites in the head and neck, frozen sections of salivary gland lesions have yielded the least reliable results. His analysis of 1629 salivary gland tumours from 17 reports since 1958, showed that the failure rate for differentiating benign from malignant tumours by frozen sections (false-negative diagnoses) was 3.7% and that false-positive diagnoses (benign tumours misdiagnosed as malignant) were made in 1% of cases. Mistakes in categorization were made in 2.6%. In the series of 229 salivary gland tumours reported by Gnepp et al (1987), mucoepidermoid carcinoma was the single most common source of false-negative results (34%), whilst pleomorphic adenomas were the most common cause of false-positive results (58%). Not unexpectedly, benign lymphoepithelial lesions also caused difficulties and this problem is likely to be greater in HIV-positive patients with cystic lesions.

The great variety of salivary gland tumours and their subclasses makes the chances of incorrect categorization by frozen sections greater than by conventional sections. However, it may be argued that this may be less important than first appears, since the optimal mode of treatment of individual tumour types is frequently uncertain.

Factors affecting accuracy of diagnosis by frozen sections

Assuming that the technique is adequate, sampling errors form the greatest obstacle to accurate diagnosis of salivary gland lesions by means of frozen sections. This is a result of the variety of configurations within a single specimen and, in particular, the presence in many of these tumours of ducts which do not appear to be neoplastic.

Another major difficulty is caused by a localized area of malignant change in a pleomorphic adenoma. This problem is still greater in a large tumour. Even if dysplastic cells are found, it is not possible to make the diagnosis of carcinoma in pleomorphic adenoma unless an area of invasion is found. If this fails, diagnosis may have to be deferred until more extensive sampling can be carried out with conventional sections.

Sampling errors of this sort can be reduced by close naked-eye examination of as many areas as possible of the whole tumour for ill-defined sectors of its borders. In any case, the specimen for frozen-section examination should include part of the capsule and
immediately contiguous gland tissue.

To distinguish non-neoplastic from neoplastic cysts, it is essential to examine any areas of mural thickening. This is particularly important in the case of mucoepidermoid carcinomas which, more frequently than any other type of tumour, can consist of mural thickenings in the wall of a single large cystic cavity.

Necrosis is a feature of malignant rather than benign tumours. Its presence should be regarded as a warning sign and area immediately adjacent to foci of necrosis should also be sampled. The main exceptions are the rare infarcted (infected) variant of Warthin's tumour (see Chapter 6) and occasional necrosis in pleomorphic adenomas.

Fine-Needle Aspiration (FNA) Cytology

Fine-needle aspiration cytology offers at least the possibility of preoperative diagnosis of parotid tumours without the risk, associated with open biopsy, of seeding tumour cells in the incision. Its limitation, which is even greater than for frozen sections, is that of missing a critical area within, or at, the border of the tumour mass and thus failing to obtain a truly representative sample. Using FNA, a small area of malignant change in a pleomorphic adenoma could easily be missed and it would not, for example, be possible to differentiate follicular from diffuse lymphomas. Aspirates of non-neoplastic lymphocytes could come from a variety of lymphocyte-rich lesions such as Warthin's tumour, tuberculosis or benign or HIV-associated lymphoepithelial lesions (Figs 2.21 to 27).

Apart from special problems such as these, it should be possible to differentiate malignant from benign salivary gland tumours with over 90% accuracy (Chen et al, 1988). Accuracy of diagnosis may be improved by application of immunohistochemistry, but electron microscopy of the aspirated material is of no value for rapid diagnosis.

A more important consideration, however, is whether fine-needle biopsy is as safe as has been believed. Increasing experience with other tumours suggests that seeding of tumour cells along the needle track is real, rather than a theoretical possibility. This has not as yet been shown in the case of salivary gland tumours, but the slow growth of pleomorphic adenomas in particular may mean that in due course such recurrences may yet be reported.

Salivary Gland Function Tests

Flow-rate studies may be useful in the investigation of xerostomia, the complaint of which is not always substantiated by objective measurements. Conversely, salivary flow may be impaired but not mentioned or may go unnoticed by the patient. Salivary flow rates, unless the mouth is obviously dry, may therefore be valuable in the diagnosis of Sjögren's syndrome as may autoantibody studies and haematological investigation. Frequently, this has been done by cannulation of the parotid duct and measuring the amount of saliva over a standard period, before and after stimulation with 10% citric acid. A stimulated parotid flow rate for normal adults over 40 years of age is approximately 1.5 mL/min. Flow rates of 0.5 mL/min or less indicate significant xerostomia. Sialometric methods are discussed in Chapter 5, but measurement of unstimulated flow of whole saliva over a defined period is adequate for most purposes and may be at least as informative as more complicated methods.
Sialochemistry

Changes in the chemical constituents of saliva have been described in Sjögren's syndrome for example. However, sialochemistry has more value in the investigation of systemic diseases such as cystic fibrosis, than in the diagnosis of primary salivary gland diseases. It has also been suggested that compliance with instructions about the taking of some drugs such as lithium can be readily monitored by saliva concentrations. Some of the uses of sialochemistry are discussed by Seifert et al (1986) and diagnostic uses of saliva have been reviewed by Mandel (1990) and is also discussed in Chapter 5.

Bacteriology

Bacteriological investigation of saliva is obviously important in the management of acute bacterial sialadenitis. Many such cases are caused by penicillinase-resistant staphylococci. Nevertheless, to use a drug such as flucloxacillin on this assumption, may delay resolution if the causative bacteria is insensitive to this narrow-spectrum antibiotic.

A fresh specimen of saliva from the duct of the affected gland should therefore be obtained before antibiotic treatment is started, as discussed in Chapter 4.

The presence of a variety of viruses in the saliva, most notably the Epstein-Barr virus, has been reported, but such investigations are generally of research value only.

Haematology

Haemoglobin levels and routine blood pictures are a necessary preoperative investigation when salivary gland surgery is contemplated. Occasionally, the blood picture may help in the diagnosis of salivary gland disease. For example the erythrocyte sedimentation rate may be raised and there may be a normochromic normocytic anaemia in Sjögren's syndrome (Chapter 4). Alternatively, lymphopenia may suggest that a salivary gland lesion is the result of HIV infection.

Autoantibody and other immunological investigations

Autoantibody studies are of particular value in patients with benign lymphoepithelial lesion to determine whether or not a connective-tissue disease is associated or whether the patient has Sjögren's syndrome. The findings of Gleeson et al (1986) also suggest that the risk of development of lymphomatous change in benign lymphoepithelial lesion is greater in patients with rheumatoid arthritis. This finding is in keeping with the significantly higher incidence of lymphoma in patients with rheumatoid arthritis compared with the normal population.

Detection of immunodeficiency is of theoretical value in recognizing patients with HIV-related salivary gland disease. However, it is simpler and more informative to determine (if possible) whether the patient is HIV antigen- or antibody-positive. If not, a simple blood picture showing otherwise unexplainable lymphopenia is strongly suggestive.
The Pathology and Surgery of the Salivary Glands

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Chapter 3: Developmental anomalies, cysts and infiltrations

The main developmental anomalies of the salivary glands are aplasia of glands, atresia of ducts, accessory or ectopic glands, and a variety of cysts. Other types of cysts are acquired but both developmental and acquired cysts are described here.

Congenital tumours such as haemangiomas and embryomas are described in Chapter 8.

Developmental Anomalies

Aplasia and duct atresia of salivary glands

Aplasia of one or more glands has been reported but is exceptionally rare. Even more rarely, it is complete and then results in total failure of secretion of saliva and its complications. Though salivary gland aplasia may be a feature of some congenital syndromes, it is not usually a significant feature of anhydrotic ectodermal dysplasia.

Duct atresia is less uncommon and may affect the submandibular duct. A cyst may develop as a consequence.

Accessory salivary glands

Accessory parotid tissue is so common as almost to be within the limits of normal. It has been found in 20% of persons by Polayes and Rankow (1979). This tissue which forms one or more lobules, lies along the line of, and is closely related to, the parotid duct, into which its ducts open. It has the same histological structure as the parotid gland and suffers from the same tumours and other diseases, though considerably less frequently. A small tumour of accessory parotid tissue may be made more apparent when the mouth is opened and the forward movement of the mandibular condyle or coronoid process displaces the mass outwards.

Ectopic and aberrant salivary tissue

Ectopic salivary tissue can form within the developmental areas of the first and second branchial arches, in the lateral part of the neck, pharynx or middle ear. Salivary tissue is frequently present in lymph nodes or extranodal lymphoid tissue particularly in the parotid and adjacent regions and this is more important from the practical viewpoint as the appearances may be mistaken for nodal metastases.

More rarely, ectopic salivary tissue may be found in a variety of sites within the head and neck region, ranging from the gingivae to the brain.
An uncommon anomaly known as a Stafne bone cyst (Fig. 3.1) as a result of its radiological appearance, is formed by invagination into the bone of the lingual aspect of the angle of the mandible, by a lobe of the submandibular gland. More rarely, normal salivary tissue may be found within the anterior mandible and Buchner et al (1991) were able to find 20 reports and presented four more of the abnormalities. They are seen radiographically as round, sharply defined cyst-like areas of radiolucency.

Intraosseous salivary gland tumours of the jaw are a recognized but rare entity (Chapter 8) and presumably arise from these foci of ectopic tissue. Even more rarely, tumours may develop in any other sites of ectopic salivary gland tissue.

Ectopic salivary tissue lacking an excretory duct can rarely give rise to salivary fistulas.

**Polycystic Disease of the Parotid Glands**

This rare anomaly described by Seifert et al (1981) may be unilateral or bilateral. Seifert et al (1986) found 2 cases among 8000 salivary gland lesions in the Göttingen Registry and there has been 1 case among 3500 salivary gland tumours in the BSGTP material. This last case was reported and illustrated in detail by Dobson and Ellis (1987).

Clinically, salivary gland enlargement is typically present in childhood and the swelling may increase in size at meal times. Sialography shows a snowstorm appearance resembling punctate sialectasis. Operation and diagnosis may however be delayed until adult life and the second case reported by Seifert et al (1981) did not present until the age of 56 years.

**Microscopy**

Though the normal architecture of the parotid may be preserved, almost the whole of the gland may be occupied by cysts of varying size, which distend the lobules. Between the cysts, there are residual serous acini and normal interlobular septa and excretory ducts (Fig. 3.2).

The cysts are lined by a single layer of flattened, cuboidal or columnar cells (Fig. 3.3). In the case reported by Dobson and Ellis (1987), the columnar cells had more abundant eosinophilic cytoplasm than intercalated duct lining cells and had rounded lumenal cell borders. Large amounts of stainable lipid may be present in the epithelial cells.

In places, the cyst-lining cells may be heaped up to give a pseudopapillary appearance. Occasionally, both distended acini and striated ducts can be seen opening into the cysts, while in remaining intact acini the ducts may be dilated (Fig. 3.4). Inflammatory changes are absent unless there has been secondary infection.

Eosinophilic amorphous material is present in many of the cyst cavities and also there are typically, rounded concretions with a concentric laminated or radial pattern or conglomerates of smaller bodies. They are strongly eosinophilic and PAS-positive. They also stain with Congo red and show the apple-green birefringence characteristic of amyloid.
Electron microscopy shows only the cuboidal cyst lining cells to have features of intercalated duct epithelium. It also confirms the fibrillar structure of amyloid in the spheroliths.

**Behaviour and prognosis**

Polycystic disease of the parotids appears to be completely benign but removal of the glands may be necessary for cosmetic reasons or for confirmation of the diagnosis. As Dobson and Ellis also note, there was similar polycystic disease in ectopic salivary tissue in the cervical lymph nodes and this could have given rise to the mistaken diagnosis of metastatic adenocarcinoma.

**Congenital Sialectasis of the Parotid Glans**

This rare anomaly described by Becker et al (1960) is characterized by ectasia of ducts which, however, open into an otherwise intact duct system. The dilated ducts are lined by a thin layer of flattened epithelium but are distinguishable from acquired duct dilatation only by the absence of any inflammatory infiltrate.

**Congenital and Acquired Cysts of Salivary Glands**

**Ranulae**

The superficial mucous retention cysts of the floor of the mouth may be congenital or acquired and may therefore be found, rarely in the newborn, or more frequently in adults.

Clinically, a ranula forms a superficial translucent swelling in the floor of the mouth with a frog's belly appearance and usually just to one side of the midline. One characteristic effect is to cause loud snoring and it can, if large enough, displace the tongue and interfere with swallowing.

Occasionally, these cysts rupture spontaneously or as a result of unnoticed trauma, to release thick viscid mucus. Recurrence is then common.

**Microscopy**

Ranulae are usually lined by a flattened layer of modified duct epithelium which may be cuboidal or columnar or there may be squamous metaplasia (Fig. 3.5). There is frequently an inflammatory infiltrate in the walls and the cyst may be multilocular.

Treatment should be by dissecting out the cyst together with the sublingual gland if recurrence is to be avoided. Alternatively marsupialization may be successful.

**Plunging ranula**

This is something of a misnomer in that it may not have the frog-belly appearance of a simple ranula, nor is it of the same nature. Plunging ranula is considerably more uncommon than the simple variety.
Clinically, a plunging ranula forms a painless swelling in the submandibular or submental triangle and may be associated with a swelling in the floor of the mouth. Microscopically, a plunging ranula is a mucous extravasation cyst, the wall of which consists of loose cellular connective tissue and which is infiltrated by inflammatory cells. There may be adjacent pools of mucus also surrounded by inflamed connective tissue.

**Treatment**

Removal of the cyst together with its parent salivary tissue should be carried out as, until recently, there has been no diagnostic measure which reliably differentiates a plunging ranula from clinically similar swellings such as thyroglossal cysts, cystic hygromas or dermoid cysts. However, computerized tomography scanning appears capable of making this distinction.

Nevertheless, dissecting out a plunging ranula is surgically difficult, particularly if there have been earlier attempts, and as a result other methods such as insertion of a grommet or even irradiation have been suggested in the past. The value of inserting a grommet has not been tested on any scale but radiation is clearly inadvisable for this benign condition.

**Mucocoeles (mucous extravasation and retention cysts)**

**Mucous extravasation cysts**

These are by far the most common type of mucocoeles of minor salivary glands. The most frequent identifiable immediate cause is trauma, frequently unnoticed or forgotten, causing tearing of a duct and extravasation of mucous into the surrounding tissues.

Clinically, the most common site is the lower lip, but can be the buccal mucosa, floor of the mouth or almost any other site within the mouth. The swelling is dome-shaped, bluish, with a thin, readily ruptured roof and typically a little over a centimetre in diameter (Fig. 3.6). In their earlier stages however the swellings appear solid.

The peak age incidence is in the second and third decades.

Microscopically, mucous extravasation cysts in their early stages consist of poorly circumscribed pools of extravasated mucus surrounded by granulation tissue or loose vascular connective tissue infiltrated by inflammatory cells and macrophages (Fig. 3.7). If the deposits of mucus are inconspicuous, the true nature of these lesions may be missed and they may be interpreted as purely inflammatory. However, the diagnosis can readily be made if muciphages are identified and occasionally mucus can be seen escaping from a damaged duct (Fig. 3.8). The minor salivary gland of origin can also frequently be seen adjacent to the lesion.

Later, the pools of mucus coalesce until there is typically no more than a single cyst with a wall of compressed connective tissue with a patchy chronic inflammatory cellular infiltrate (Fig. 3.9).

The cyst should be excised complete with its underlying salivary gland.
**Mucous retention cysts**

These have a lining of compressed ductal epithelium and are comparatively uncommon (Fig. 3.10). They are not distinguishable clinically from mucous extravasation cysts and are treated in the same way.

**Subepithelial mucocoeles**

Rarely, mucocoeles are so superficial as to be immediately subepithelial (Fig. 3.11). If their origin from salivary tissue is not apparent, these lesions can mimic microscopically and clinically, the bullae of such diseases as mucous membrane pemphigoid.

Limited resection of the cyst and underlying gland is curative.

**Salivary duct cysts**

Though microscopically similar to mucous retention cysts of minor glands, salivary duct cysts differ in that they mainly form in the parotid glands, usually in elderly men. These cysts are usually unilocular and rarely exceed 2-3 cm in diameter.

**Microscopy**

The modified duct epithelium lining the cysts may be flat and multilayered (Fig. 3.12). Occasionally it may show oncocytic change or rarely, squamous metaplasia. There may be spherolith formation in mucoid cyst contents.

There is typically only sparse inflammatory infiltration of the cyst walls but small granulomas may form as a result of extravasation of mucus. Increase in size of the cyst can lead to obstructive sialadenitis.

Complete removal of the cyst, with care to preserve the facial nerve, is indicated.

**Lymphoepithelial cysts**

Lymphoepithelial cysts are uncommon and are unusual in that they mainly affect the parotid glands but can also form in the floor of the mouth.

The essential microscopical features are those of an epithelium-lined cyst in the centre of a dense aggregate of lymphoid tissue of similar cellular composition to a lymph node and which usually contains follicles (Fig. 3.13).

The epithelial lining of these cysts is variable in character though usually flattened but multilayered. It sometimes contains goblet cells or rarely, sebaceous cells. The cyst contents are serous and typically contain desquamated epithelial cells, foam cells and lymphocytes in varying numbers. Cholesterol clefts and granuloma formation may be seen in the stroma.

Lymphoepithelial cysts should be excised completely. However, these cysts should be distinguished from the lymphoepithelial cysts seen in patients with HIV infection. These are
discussed below and in more detail in Chapter 4.

**Branchial cleft cysts**

These congenital cysts lie along the line of the anterior border of the sternomastoid muscle and controversy persists as to whether or not they are different entities from lymphoepithelial parotid cysts, as discussed by Verbin and Barnes (1985). Microscopically, these two types of cyst cannot be distinguished but it seems likely that lymphoepithelial cysts in the parotid gland result from cyst formation in intranodal epithelial inclusions.

Branchial cleft cysts present frequently in children as a consequence of recurrent infection. Incision and drainage in the acute stage should be avoided, because of the risk of damage to the facial nerve. The cyst should therefore be aspirated and appropriate antibiotic treatment given. Elective superficial parotidectomy can be carried out when the inflammation has completely subsided. This may be exceedingly difficult because of local fibrosis and the small size of the child's facial nerve.

Branchial cleft cyst carcinoma is a rarity and discussed by Foss *et al* (1991), it is also controversial whether it arises as a result of malignant change in the lining or is a metastasis from a tonsillar carcinoma or other occult primary.

**Lymphoepithelial cysts associated with HIV infection**

Elliot and Oertel (1990) have reviewed 14 lymphoepithelial cysts from salivary glands. All were in lymph nodes and lined by squamous epithelium. There was a mixed mononuclear cell infiltrate but multinucleate giant cells were present in four cases. All five of the patients tested for HIV infection were positive.

These cysts resemble benign lymphoepithelial lesion in many respects but for the cavity which may form a major part of the mass. In some cases, the lesion is almost entirely cystic with no more than nodules of lymphoplasmacytic tissue, forming mural thickenings. Also unlike benign lymphoepithelial lesion, they predominantly affect young adults males and when seen in such patients are strongly suggestive of HIV infection. These lesions are described in more detail in Chapter 4.

**Infiltrations and Miscellaneous Salivary Gland Diseases**

The following are considered here:

1. Lipomatosis
2. Onocytosis
3. Mikulicz syndrome
4. Amyloidosis
5. Iron deposition
6. Uric acid deposition

7. Familial combined hyperlipidaemia.

**Lipomatosi**

Fat cells are a normal component of the parotid glands and can sometimes be found in the submandibular glands. The fat content of these glands increase with age (Fig. 3.14). Overgrowth of fatty tissue in the salivary glands may result from diabetes mellitus or severe obesity. In such cases, the fat is distributed interstitially, spreads to gland parenchyma apart and can give rise to a swelling. Tissue reduction by conservative surgery may then be required for cosmetic reasons.

Fatty replacement can also follow parenchymal atrophy from any cause. Seifert (1959) has described virtually complete replacement of parotid tissue by fat (lipomatous parotid atrophy) and compares it with a similar phenomenon in the pancreas of infants, a condition thought to result from early viral infection, particularly with coxsackie B viruses which may have a role in some cases of early onset insulin-dependent diabetes mellitus.

**Oncocytosis**

Focal areas of oncocyctic change in salivary glands and ducts becomes increasingly common with age (Fig. 3.15). Taked (1993) in a postmortem study of minor salivary glands from 217 cadavers found oncocyctic change progressively more frequently with age until after 81 years, 100% were affected. It was more frequent in the duct system, and particularly in the interlobular ducts. Oncocytic hyperplasia (oncocytosis) also became more frequent with age with a peak frequency of 14.7% between the ages of 61 and 70 years. Occasionally, it becomes widespread and can be mistaken for an oncocyteoma as discussed in Chapter 6.

**Mikulicz syndrome**

This term is sometimes given to widespread, bilateral enlargement of salivary and sometimes, lacrimal glands as a result of diseases such as infiltration by lymphoma or lymphocytic leukaemia, sarcoidosis, sialosis or other definable diseases. The term 'Mikulicz disease' is sometimes given to the condition more generally known as benign lymphoepithelial lesion as described in Chapter 8. Both of these terms should be avoided as they are a source of confusion.

**Amyloidosis**

Deposits of amyloid can be found in pleomorphic adenomas and possibly other epithelial tumours of salivary glands, but amyloid can also be deposited in otherwise normal salivary glands as a result of systemic amyloid disease. In amyloidosis secondary to immunocyte dyscrasias (characterized by AL-type amyloid - formerly termed 'primary amyloidosis') various parts of the gastrointestinal tract are frequently involved. However, in a series of 229 cases Kyle and Greipp (1983) and in an earlier, detailed review of 236 cases (mainly of AA-type amyloidosis) Kyle and Bayrd (1975) did not note any salivary gland dysfunction clinically, though these glands were not specifically investigated. In reactive
systemic amyloidosis associated with chronic inflammatory diseases (characterized by AA-type amyloid and formerly termed 'secondary amyloidosis'), the liver, kidney and spleen are most likely to be involved. The apparent absence of salivary gland involvement may also be noted in the clinicopathological investigation of 131 cases of different types of amyloidosis, of which 76 were of AA-type, by Browning et al (1985).

There have also been several studies on the oral manifestations of amyloidosis and an extensive autopsy study was carried out by Van der Wal et al (1984) who also reviewed previous reports. Macroglossia is the main oral effect of systemic amyloidosis, but even these studies do not appear to have noted any salivary gland involvement in terms of swelling or diminished secretion.

The rarity of substantial deposits of amyloid in salivary glands is emphasized by the fact that the report of a localized primary amyloid tumour-like mass in a parotid gland by Stimson et al (1988), was claimed to be the first such case in the English literature. This patient, a man of 65 years, had a painless parotid swelling of one year's duration but was otherwise well and had no detectable systemic abnormalities. The patient remained well at one year later.

In a woman of 58 years with xerostomia and xerophthalmia, reported by Gogel et al (1983), no autoantibodies suggestive of Sjögren's syndrome could be detected, but minor salivary gland biopsy showed gross amyloid deposition and acinar atrophy. Biopsy of other organs showed widespread amyloidosis (Adelta VI type), from which she died three months afterwards.

Despite the paucity of reports of significant deposits of amyloid in the major salivary glands of patients with amyloid disease, Delgado and Mosqueda (1989) have reported that in 19 patients with secondary amyloidosis, amyloid deposits were found in the labial salivary glands in all cases.

**Microscopy**

The gland parenchyma is progressively replaced by homogeneous eosinophilic material with the staining properties of amyloid (Fig. 3.16), a patchy inflammation and sporadic giant cells (Fig. 3.17). The amyloid also shows the characteristic birefringence in polarized light (Fig. 3.18). In the cases of secondary amyloidosis reported by Delgado and Mosqueda (1989), the deposits in the labial glands were not immediately obvious in haematoxylin and eosin-stained sections but were made apparent by Congo red and crystal violet staining. The distribution was periductal in all cases, and also periacinar in 84%, perivascular in 68% and interstitial in 37%. The amount of deposit ranged from a thin periductal layer to massive infiltration of the gland.

It seems, therefore, that amyloid deposition is unlikely to cause any significant clinical sign or symptoms of salivary gland dysfunction. However, detection of amyloid in the labial glands, as suggested by Delgado and Mosqueda (1989), may be a highly sensitive method of diagnosis in secondary amyloidosis. If, therefore, amyloid deposition is found by chance in salivary glands and is not associated with a tumour, then the patient should be investigated for possible causes of systemic amyloidosis.
Iron deposition

Iron deposits in the salivary glands can be found in haemochromatosis and a resulting sicca syndrome has been reported by Blandford et al (1979) and also by Vrielinck (1988) in a patient with myelodysplastic syndrome and transfusion-related haemochromatosis.

Iron deposits are likely to be more frequently found in thalassaemia since, worldwide, this is a far more common disease. In thalassaemia, iron deposition in salivary tissue may also be associated with a sicca syndrome. In a 20-year-old male with thalassaemia minor, reported by Borgna-Pignatti et al (1984), the disease had been diagnosed 19 years earlier and heavy deposits of iron were found in the labial salivary glands.

Microscopy

The salivary glands show acinar atrophy, interstitial fibrosis and brownish deposits of iron particularly in the periphery of the acinar and duct cells (Fig. 3.19). The nature of these deposits is readily confirmed by Prussian blue (Perl) staining (Fig. 3.20).

Uric acid deposition

Eilon et al (1982) have reported a patient with hyperuricaemia and a recurrent, mildly painful parotid swelling in a 26-year-old man. Microscopic analysis of the saliva from the swollen gland showed uric acid crystals and the salivary uric acid was the same as that of the serum (9.6%).

Lowering the serum uric acid level with probenecid resulted in improvement in the symptoms and it was suggested that the deposition of uric acid crystals in the salivary ducts had led to recurrent episodes of obstruction and infiltration.

Familial combined hyperlipidaemia

Xerostomia may be a major complaint in patients with type V hyperlipidaemia (raised cholesterol, triglyceride, chylomicron, and very-low-density lipoprotein levels) as reported by Reinertsen et al (1980). Salivary gland scans suggest that focal inflammatory infiltrative lesions and obstructions may be present.
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 reinsertion 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.
Tuberculosis 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 radiocontrast 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 mm\(^2\), 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></td>
<td></td>
</tr>
<tr>
<td>precipitin</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;</td>
</tr>
<tr>
<td></td>
<td>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 gammapathy |
| 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 beta2-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 epimyoeptihelial 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 Calebresi 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.

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>Sex</td>
<td>Females:males = 9:1</td>
<td>Predominantly males</td>
</tr>
<tr>
<td>Age</td>
<td>Usually &gt; 50 years</td>
<td>Usually 20-40 years</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Typically absent</td>
<td>+++</td>
</tr>
<tr>
<td>Xerostomia/xerophthalmia</td>
<td>++</td>
<td>Frequently absent</td>
</tr>
<tr>
<td>Cystic salivary gland lesions</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>RF, ANF, SS-A and SS-B</td>
<td>None characteristic for Sjögren's syndrome</td>
</tr>
<tr>
<td>Lymphatic infiltrate</td>
<td>CD4</td>
<td>CD8</td>
</tr>
<tr>
<td>HLA</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 hyperchromatitic 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 10^9/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 corneal transplantation.

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


The amount of saliva secreted and to a large extent, its composition, are normally controlled by the autonomic nervous system. Other factors can also interfere with function, namely drugs affecting autonomic responses, deficiency of fluid, and disease or destruction of the gland parenchyma.

Autonomic Control of Salivary Gland Function

Garrett (1987) has carried out extensive animal experimentation in this field. His main conclusions are that normal reflex secretion of saliva depends on centrally coordinated parasympathetic and sympathetic activity.

Parasympathetic impulses
- usually evoke most of the fluid secreted;
- cause variable degrees of exocytosis of some cells;
- induce contraction of myoepithelial cells;
- cause vasodilatation as part of the secretory process.

Sympathetic impulses
- are more intermittent;
- act essentially on cells receiving parasympathetic impulses and tend to have synergistic effects;
- frequently do not cause much modulation of fluid;
- tend to modulate the composition of saliva by increasing exocytosis from certain cells;
- usually induce contraction of myoepithelial cells;
- some sympathetic fibres exercise tonic effects on blood vessels; these fibres are likely to be under separate central control and not involved directly in the reflex secretory pathway.

Mechanisms of Salivary Secretion

The mechanisms of saliva secretion have been reviewed in detail by Baum (1993) who emphasizes that much of the information (as presented below) comes from study of rat salivary glands. Little is known of the mechanisms of human salivary secretion but such data as exists generally conform to the broad principles discussed here.

As Baum (1993) has described, saliva is produced only in response to neurotransmitter stimulation. Neurotransmitters probably bind to specific receptors in the basolateral region of the acini. Noradrenaline binds to both alpha- and beta-adrenergic receptors while acetylcholine binds to cholinergic receptors. These receptors depend on G-protein (guanine nucleotide-binding regulatory protein) for transduction of the neurotransmitter stimuli. The G-proteins that carry the stimuli into the acinar cells are heterotrimeric molecules consisting of alpha-,
beta- and gamma-subunits. The alpha-subunit is the site of guanine nucleotide binding and probably conveys the functional specificity to a G-protein. Binding of a neurotransmitter to a receptor greatly strengthens the ability of a receptor to associate with a G-protein. The association with a G-protein stimulates in turn, replacement of GDP by GTP at the nucleotide binding site and promotes dissociation of the heterotrimer into a free alpha-subunit and a betagamma complex. The alpha-subunit can then activate the appropriate receptor molecule. Activation continues until the GTP is broken down into GDP by endogenous enzymic (GTPase) activity in the alpha-subunit. The GDP bound to the alpha-subunit then unites with the betagamma complex to regenerate the heterotrimeric molecule. There is also some evidence to suggest that the betagamma complex or even the beta-subunit alone may be able directly to activate some receptor molecules. The best recognized signal transduction processes in salivary glands are first, generation of cAMP as a result of beta-adrenergic receptor stimulation and second, formation of 1,4,5-inositol triphosphate (IP₃) after acetylcholine receptor stimulation. The latter leads to calcium-ion mobilization and, as a consequence, fluid secretion.

The specific mechanism by which cAMP acts as an intermediary in protein exocytosis remains unclear. Typically, cAMP elicits a response by activation of cAMP-dependent protein kinase and protein phosphorylation. In rat salivary gland, beta-adrenergic receptor stimulation leads to a rise in cAMP levels, activation of the A-kinase, phosphorylation or dephosphorylation of several cellular proteins and thus amylase or glycoprotein secretion by the parotid or submandibular glands, respectively. Indeed, treatment of rat parotid and submandibular gland cells with cAMP analogues also leads to protein secretion. Kinetic analyses suggest that the 24-26 kDa species protein is the most probable candidate for phosphorylation though its function in protein exocytosis is unknown. Moreover, the role of A kinase-dependent phosphorylation in rat parotid gland protein secretion has become somewhat controversial.

It is well established that Ca²⁺ plays a central role in fluid secretion by acinar cells in response to acetylcholine receptor stimulation. Activation of this receptor leads to fluid-related signal transduction via coupling to a G-protein often designated Gp. The latter is probably a member of the Gq/11 family which is known to couple to phospholipase C. Activation of phospholipase C results in hydrolysis of a minor membrane phospholipid, phosphatidylinositol 4.5-biphosphate, and formation of second messengers IP₃ and diacylglycerol. IP₃ is the main mediator of Ca²⁺ mobilization and thus of fluid secretion, but diacylglycerol can promote activation of protein kinase C and lead to stimulation of a minor exocytic pathway.

IP₃ binds to a receptor protein located on an intracellular Ca²⁺ storage pool that is probably related to, or part of, the endoplasmic reticulum. The IP₃ receptor also functions as a Ca²⁺ release channel and allows stored Ca²⁺ to move down a concentration gradient into the cytoplasm. These Ca²⁺ levels quickly rise approximately tenfold as a consequence of acetylcholine receptor stimulation. This reaction triggers a cascade of event which include sustained Ca²⁺ entry and activation of specific ion-transport pathways. Generation of fluid in the acinar lumen is the final result, by mechanisms discussed in detail by Turner (1993).
Extracellular Ca\(^{2+}\) and entry of Ca\(^{2+}\) sustain high levels of salivary fluid secretion over long periods. However, mechanisms of Ca\(^{2+}\) entry into acinar cells which are non-excitable and not voltage-activated, are poorly understood. Possible mechanisms for Ca\(^{2+}\) entry into acinar cells include a direct receptor-gated Ca\(^{2+}\) channel, a G-protein-activated Ca\(^{2+}\) channel, and a second messenger-activated Ca\(^{2+}\) channel. However, there is little evidence for the involvement of the first two of these mechanisms and only a few reports have suggested that Ca\(^{2+}\) entry may be activated by the synergistic action of IP\(_3\) and its metabolite 1,3,4,5-inositol tetrakisphosphate (IP\(_4\)).

Currently, the most favoured explanation of the mechanism of Ca\(^{2+}\) entry appears to be the one termed 'capacitative Ca\(^{2+}\) entry'. This suggests that depletion of the Ca\(^{2+}\) storage pool provides the driving force for sustained Ca\(^{2+}\) entry. Support for this theory comes from studies that have shown that graded depletion of the Ca\(^{2+}\) store has led to similarly graded Ca\(^{2+}\) entry. Use of non-receptor activation by, for example, thapsigargin, to deplete the Ca\(^{2+}\) store also leads to Ca\(^{2+}\) entry. Though the exact mechanism by which depletion of Ca\(^{2+}\) stores causes Ca\(^{2+}\) entry is uncertain, it is clear that it can be modulated by extracellular pH and cytoplasmic Ca\(^{2+}\).

Acinar cells are responsible for production of the fluid component of saliva and most of the proteins that it contains. The acinar cells are water-permeable and derive fluid from the surrounding blood vessels. The fluid is carried by the duct system which is impermeable to water. During passage through the ducts, there is exchange of electrolytes. Most of the Na\(^+\) and Cl\(^-\) ions are removed, but some K\(^+\) and HCO\(_3\)\(^-\) ions as well as a little protein, are added.

**Primary fluid secretion in salivary acini**

As in all secretory epithelia, fluid transport in salivary gland cells is thought to be driven osmotically by transepithelial salt gradients. Turner (1993) has explained that studies on rat and rabbit salivary glands have suggested three mechanisms for primary salivary fluid secretion. Unexpectedly, these mechanisms do not appear to be alternative explanations for salivary fluid secretion, but appear to operate concurrently within the same gland or possibly within the same acinar cells.

The first mechanism, of which the other two can be regarded as variations, is that fluid secretion depends on the combined action of four membrane-transport systems, namely: (i) an Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter that is located in the basolateral membrane of the acinar cells; (ii) a basolateral Ca\(^{2+}\)-activated K\(^+\) channel; (iii) an apical conductive pathway for Cl\(^-\) which is presumably a Ca\(^{2+}\)-activated Cl\(^-\) channel; and (iv) the Na\(^+\)/K\(^+\) ATPase.

In the resting state, both K\(^+\) and Cl\(^-\) are concentrated in the acinar cell above electrochemical equilibrium, with K\(^+\) being concentrated by Na\(^+\)/K\(^+\) ATPase and Cl\(^-\) by Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter. As discussed earlier, secretagogue stimulation leads to a rise in intracellular Ca\(^{2+}\) concentration and in turn, opening of the basolateral Ca\(^{2+}\)-activated K\(^+\) channel and the apical Cl\(^-\) channel. Increases in K\(^+\) and Cl\(^-\) conductance allow KCl to flow out of the cell and this results in accumulation of Cl\(^-\) ions and their associated negative electrical charge in the acinar lumen. As a consequence, electrical attraction causes Na\(^+\) to
leak from the interstitium through the tight junctions to follow Cl⁻. The resulting osmotic gradient for NaCl causes transepithelial movement of water from the interstitium to the lumen. Continued influence of an agonist results in a transepithelial chloride flux and concomitant fluid secretion. This is sustained by Cl⁻ entry via Na⁺-K⁺-2Cl⁻ cotransporter and exit via the apical Cl⁻ channel. Removal of the stimulus is followed by a fall in intracellular calcium concentration to resting levels, closure of the K⁺ and Cl⁻ channels and return of the cell to its resting state.

The second mechanism is similar except that the basolateral Na⁺-K⁺-2Cl⁻ cotransporter is replaced by a Cl⁻/HCO₃⁻ exchanger acting in parallel with an Na⁺/H⁺ exchanger. A fall in intracellular Cl⁻ concentration as a result of secretagogue KCl loss, thus leads to entry of more Cl⁻ in exchange for HCO₃⁻ acidification of the cytoplasm. This HCO₃⁻ loss is buffered by the Na⁺/H⁺ exchanger which uses the extracellular-to-intracellular Na⁺ gradient generated by Na⁺/K⁺-ATPase, to drive protons out of the cell.

Unlike the first two mechanisms in which Cl⁻ is the secreted ion, the third involves acinar HCO₃⁻ secretion. In this last mechanism, CO₂ enters the acinar cell across the basolateral membrane and is converted to HCO₃⁻ plus a proton, by intracellular carbonic anhydrase. The HCO₃⁻ is lost across the apical membrane via an anion channel which is possibly the same as that involved in Cl⁻ secretion. The proton is expelled by the basolateral Na⁺/H⁺ exchanger.

**Antibacterial Substances in Saliva**

Molecules such as lysozyme, thiocyanate-dependent factors and lactoferrin can be shown to have antibacterial activity *in vitro*. Other factors which might affect bacterial activity in the oral cavity are the pH and buffering capacity of saliva and its content of immunoglobulins.

Despite the presence of these substances, the oral cavity supports a flourishing population of microbes including a great variety of pathogens. Dental caries is usually also active on a high sugar diet and periodontal disease is likely to progress unless a high standard of oral hygiene is maintained. Despite great efforts to show protection against these diseases by saliva, the findings have been unconvincing. Moreover, salivary mucins for example, may have harmful effects by promoting adhesion of bacteria to the teeth. That aside, putative effects of protective substances are difficult to substantiate in humans because of the difficulty of performing critical experiments.

It is clear that the oral cavity has a high level of local immunity. The large bony wounds resulting from extraction of teeth normally heal rapidly despite contamination by the vast and pathogenic flora that proliferates in periodontal pockets. However, this fortunate outcome is likely to result from local tissue immunity rather than from salivary components.

Another factor which may affect the nature of the bacterial flora of the mouth is bacterial competition for nutrients in their individual ecological niches rather than antibacterial substances in the saliva. However, the bacterial flora of the mouth is undoubtedly affected by low salivary flow rates which, in particular, promote cariogenic activity and the proliferation of *Candida* species. Nevertheless, xerostomia does not appear to promote periodontal disease.
The only aspect of saliva production that can be reliably related to protection against infection is that of the overall flow rate. In conditions of xerostomia, the oral bacterial flora changes and in particular Candida albicans and staphylococci are likely to flourish. Dental caries activity and mucosal infections are thus promoted.

Collection of Saliva and Measurement of Salivary Flow Rates

Saliva may need to be collected to provide a sample for assays of various types but more frequently flow rates are required for objective confirmation of xerostomia. Both unstimulated (resting) and stimulated flow can be measured. A variety of apparatus has been devised to carry out these measurements and record them automatically, but are mainly for research purposes.

Many methods have been devised and may be summarized as follows:

--> Unstimulated flow of whole (mixed) saliva.
--> Stimulated flow of whole saliva.
--> Stimulated or unstimulated flow from individual glands.

Salivary stimuli

A variety of stimulants to salivary secretion have been recommended. These are either systemic or local sialogogues. The main systemic sialogogue that has been used is the parasympathomimetic drug, pilocarpine. Though effective, pilocarpine does not precisely reproduce the balance of sympathetic and parasympathetic activity responsible for normal secretion. One consequence is that it can alter the concentrations of normal constituents, particularly sodium and potassium ions. Pilocarpine can also cause systemic cholinergic effects such as colic, diarrhoea, bradycardia and sweating which can be troublesome.

Local sialogogues are convenient and generally more satisfactory. A good example is 5% citric acid solution which is a potent sialogogue and does not interfere with the composition of the final specimen. Five drops of this solution can be dropped from a pipette or disposable syringe onto the dorsum of the tongue. This may be used as a preliminary measure before collecting unstimulated saliva. The purpose of this manoeuvre is to flush out stagnant secretions that confuse the analysis. Thus, citric acid is applied to the tongue and saliva is collected for 15 min to eliminate rest transients.

Stimulates or unstimulated saliva can then be collected for periods of 15-30 min as necessary. However, Ericson (1969) has pointed out that the results obtained by different sialometric methods are not necessarily comparable because individuals with a vigorous secretory response to one stimulus do not necessarily have a similar response to another.

Collection of mixed whole saliva

A variety of methods of collecting saliva from individual glands or collecting mixed whole saliva is available. Many of these methods require specially made equipment and are mainly suitable for research purposes.
Mason and Chisholm (1975) described the following methods:

--> Spitting
--> Drainage
--> Suction
--> Cotton-wool rolls.

More recently, Navesh (1993) has reviewed methods for collecting saliva.

**Spitting and drainage methods**

The patient is put into a comfortable sitting position with the head inclined forward and encouraged to spit at one-minute intervals or to allow saliva to drain out of the mouth into a funnel draining into a sterile collecting vessel.

**Suction**

This method requires the equipment associated with a dental chair. The patient is put into a similar position as before to allow saliva to collect into the anterior floor of the mouth. A saliva ejector is placed behind the lower incisor teeth and the secretion is trapped in a bottle intervening between the ejector and the drainage system.

**Cotton-wool rolls and other absorbent devices**

Pre-weighed cotton-wool rolls are put under the tongue for a two-minute period then taken out and reweighed. This method allows quantitation only. More recently, proprietary devices such as OraSure have been introduced to simplify saliva collection and preserve it for analysis. Its use has been reported by Thieme *et al* (1994) for collection of saliva for determination of measles, mumps and rubella immunization status. OraSure is a cotton-fibre pad which can absorb 1 mL of oral fluid. It is saturated with hypertonic saline solution, dried and mounted on a plastic handle. It is placed between the gingiva and buccal mucosa for two minutes, then withdrawn, and placed in an antiseptic transport medium. In the laboratory, the saliva specimen is recovered by centrifugation.

While there appear to be advantages to the OraSure system for gathering oral fluid, it must be appreciated that by virtue of the filtering effect of the cotton-fibre pad, it does not collect whole saliva. Cordeiro *et al* (1993) found that the levels of IgG in OraSure oral fluid were three- to fourfold higher than those of saliva, and amylase levels were two- to fourfold higher. They suggested that the cotton-fibre pad might promote passage of crevicular gingival exudate and stimulate secretion of amylase as a result of the pad's buffer solution. However, North *et al* (1993) found that the OraSure system provided a reliable index of tobacco usage by means of cotinine salivary assay.

**Collection of parotid gland saliva**

Pure parotid saliva can be collected by cannulating the parotid duct with a polythene catheter or using a suction tip.
Catheterization of the duct allows collection of uncontaminated saliva but is uncomfortable for the patient and the tube has to be held in place.

For suction, the most widely used device is the Carlson-Crittenden/Lashley cup, the centre of which is placed over the parotid papilla. The cup consists of a central chamber into which the saliva flows and an outer chamber to which suction is applied to cause the cup to adhere to the buccal mucosa (Fig. 5.1).

Collection of submandibular gland saliva

In the past, submandibular gland saliva in particular was collected by catheterizing the submandibular duct after dilatation. This technique is neither very simple nor comfortable for the patient.

Segregator appliances require to be purpose-made to fit the patient's mouth and function in the same way as the Carlson-Crittenden cup. The device, which fits the anterior floor of the mouth, has a central collecting chamber, isolated by a surrounding ridge from the outer suction chambers.

Advantages and disadvantages of collection methods

The choice of method depends on the type of investigation being carried out. If for example, the aim is to investigate viral shedding from the parotid gland, then catheterization of the duct has to be carried out or a Carlson-Crittenden cup used. Mandel (1980) has listed the variations in concentrations of sodium, potassium, calcium, magnesium, bicarbonate and phosphate ions in the secretions of individual glands and whole saliva. But, overall, his findings suggest that collection of whole saliva is satisfactory for such measurements.

For straightforward measurement of salivary flow rate for confirmation of the diagnosis of Sjögren's syndrome, in particular, the simple spitting method for unstimulated saliva over a period of 10 or 15 min, requires minimal equipment and is satisfactory. In the past, it was thought that since the parotid glands were predominantly affected by this disease, it was necessary to collect parotid saliva. However, the total activity of all salivary glands including the minor glands make a greater contribution to the amount of saliva produced under normal conditions. Stimulated parotid flow is unsatisfactory because of difficulties that some patients have with the collection devices and because of the variety of stimulants used have cause confusion as to what is meant by abnormal flow rates.

Atkinson et al (1990) assessed salivary gland function and its clinical features in 64 patients with Sjögren's syndrome (SS). They found that stimulated salivary flow rates correlated inversely with the microscopic lymphocytic focus scores in labial gland biopsies and therefore suggested that stimulated flow rate studies were a particularly useful alternative to repeated lip biopsies in long-term studies of the progress of the disease. By contrast, Saito et al (1991) found that in 113 patients with dryness of both mouth and eyes, periductal lymphocytic infiltration of labial glands was found in only 50% of those with reduced salivary flow, but correlated better with xerophthalmia and SS-A and SS-B autoantibodies (see Chapter 4). Nevertheless, Speight et al (1992) found that a whole unstimulated salivary flow rate of
≤ 0.1 mL/min was 81% predictive of Sjögren's syndrome if other causes of xerostomia could be excluded. Saliva was collected by encouraging the patients to spit gently or drool into a beaker for 15 min.

Though controversy persists about methods of saliva collection and whether or not sialogogues should be used, there is a growing body of opinion as reflected by Speight et al (1992) that collection of unstimulated mixed saliva best reflects the normal resting state. The European Community Study Group on Diagnostic Criteria for Sjögren's Syndrome (1994) have also concluded that collection of whole unstimulated saliva is the best method for confirming the degree of xerostomia (Vitali et al, 1994).

In practice, therefore, an adequate indication of salivary flow rates is obtained by putting the patient in quiet surroundings and asking them not to swallow but to expectorate all saliva into a Universal or other container over a period of 15 min. The measurement may then be repeated after stimulating the flow with a few drops of lemon juice or 5% citric acid, dropped on the tongue. Typical normal flow rates are 0.1 mL/min (resting) and 1.5-2 mL/min after stimulation with lemon juice. In established Sjögren's syndrome the stimulated flow rate is typically about 0.25-0.5 mL/min.

Unstimulated whole saliva flow rates are not merely simpler to measure but probably give a better guide to the level of discomfort felt under normal conditions by the patient.

**Changes in Composition of the Saliva**

The composition of saliva changes in disease states, particularly those causing xerostomia and these changes have been reviewed by Mandel (1990). A variety of hormones, antibodies and drugs can also be assayed in this secretion.

Hormones that can be monitored in saliva include aldosterone, cortisol, dehydroepiandrosterone, testosterone, 5alpha-dihydrosterone, 17beta-hydroxyprogesterone, progesterone, 17beta-oestradiol, oestriol, oestrone, insulin and melatonin. Salivary assay of cortisol has been reported to be more reliable than serum levels for monitoring adrenal cortical function.

It must be emphasized that most studies on the composition of saliva have been based on relatively few subjects and may therefore be biased. Differences in laboratory methods may also result in discrepancies in the results which are not, in fact, real. Other complications are the presence of enzymes which are probably of bacterial origin.

The composition of saliva in health provides a baseline for variations resulting from disease or drug administration. Unfortunately, even in healthy persons, many variables such as the following can affect the composition of saliva:

--> Flow rate.
--> Source. Saliva specifically collected from the major gland differs in composition from whole saliva which includes that secreted by the minor glands.
--> Diurnal variation.
--> Duration and type of stimulus.
Rest transients. The concentration of ions such as K⁺ may vary according to whether the saliva sample is taken shortly after stimulation or after the flow has been allowed to continue for several minutes.

Age and gender differences. Findings on differences in salivary flow and hence salivary composition, according to the age or gender of the subjects have been conflicting. Findings that, for example, salivary flow rates are lower in older females than males could conceivably be biased by the presence of unsuspected Sjögren's syndrome among the females.

Plasma levels. The concentration of many molecules in saliva is related to and varies with their plasma levels.

Diet. Findings suggesting that a predominantly carbohydrate diet, for example, leads to higher concentrations of salivary amylase or that high protein diets lead to higher concentrations of salivary amylase have not been widely confirmed or are conflicting.

Drugs. Any drug which affects salivary flow rates can affect the concentration of salivary constituents that are flow-dependent. Important drugs which affect salivary flow rates are shown in Table 5.1.

Hormonal effects. Mineralocorticosteroids affect both plasma and salivary concentrations of ions such as Na⁺ and HCO₃⁻. It has also been suggested that the concentration of some salivary constituents such as Ca²⁺ and Na⁺ may fall and K⁺ levels rise at the time of ovulation.

Constituents of saliva are shown in Table 5.2 but in view of the comments already made, these figures should be accepted with caution.

Table 5.1 Drugs liable to cause xerostomia

1. Drugs with antimuscarinic activity

   - Atropine and analogues (hyoscine, ipratropium, etc)
   - Tricyclic antidepressives
   - Monoamine oxidase inhibitors
   - Phenothiazines and related neuroleptics
   - Orphenadrine, benzhexol and related anti-parkinsonian agents
   - Antihistamines
   - Ganglion blockers and clonidine
   - Anti-emetics (antihistamines, hyoscine and phenothiazines)

2. Drugs with sympathomimetic activity

   - 'Cold cures' and decongestants containing ephedrine or phenylpropylamine
   - Bronchodilators (isoprenaline, orciprenaline, etc)
   - Appetite suppressants, particularly amphetamines and diethylpropion.

Salivary assays in diagnosis

Saliva is undoubtedly a valid medium for many diagnostic assays. Collection of saliva is non-invasive, painless and obviates the risk of needle-stick injuries. Nevertheless, most clinicians are unused to collecting saliva but practised in collecting blood which can usually be done more quickly. Moreover, most laboratories use equipment for handling blood and are
unused to dealing with saliva with its mucins and other constituents or contaminants which may affect the assays. With regard to drug assays, few current pharmacology texts even mention the possibility of using saliva.

Mandel (1993) has provided an interesting brief history of the uses of saliva in diagnosis. He has described both the value of salivary assays in diagnosis and the difficulties in getting them accepted. As he had earlier stated (Mandel, 1990) 'Saliva is not one of the popular body fluids. It lacks the drama of blood, the sincerity of sweat and the emotional appear of tears'.

**Inorganic ions**

The findings of Mandel (1980) include the following:

**Sialadenitis**

Raised Na⁺, K⁺, Ca²⁺ and PO₄⁻ levels.

**Radiation damage**

Raised Na⁺, Ca²⁺, Mg²⁺ and Cl⁻ levels.

**Sjögren's syndrome**

Raised Na⁺, Cl⁻ and PO₄⁻ in parotid gland saliva.

**Cystic fibrosis**

Raised Na⁺, Ca²⁺, and PO₄⁻ levels. Mandel (1980) suggested that the combined Ca²⁺ PO₄⁻ concentrations formed a useful diagnostic index.

**Aldosteronism**

Depressed Na⁺ but raised K⁺ levels. Mandel (1980) suggested that the ratio of Na⁺/K⁺ could form a useful diagnostic index.

**Hypertension**

Depressed Na⁺ levels.

**Alcoholic cirrhosis**

Raised K⁺ levels.

**Hyperparathyroidism**

Raised Ca²⁺ levels.
**Diabetes mellitus**

Depressed HCO$_3^-$ levels.

**Psychiatric illness** (not otherwise specified)

Raised Na$^+$ and K$^+$ levels. Mandel (1980) suggested that the product Na$^+$ x K$^+$, could form a useful diagnostic index.

**Organic components**

Mandel's (1980) findings included the following:

**Sjögren's syndrome**

Raised total protein and beta$_2$-microglobulin levels in parotid gland saliva.

**Cystic fibrosis**

Raised total proteins, amylase, lysozyme in submandibular gland saliva and glycoproteins in parotid gland saliva.

**Cirrhosis**

Raised total protein and amylase in parotid gland saliva.

**Hyperparathyroidism**

Raised total protein.

**Diabetes mellitus**

Raised total protein, IgA, IgG and IgM, and raised glucose levels.

**Sarcoidosis**

Depressed amylase and lysozyme levels.

Two diseases that have been studied in terms of sialochemistry in particular detail are Sjögren's syndrome and cystic fibrosis.

**Sjögren's syndrome**

Considerable difficulties are sometimes found in confirming the diagnosis of Sjögren's syndrome because of the great variability in the abnormalities that may be detected. The problem is well illustrated by the necessity to institute the European Community Study Group on Diagnostic Criteria for Sjögren's Syndrome. The Group concluded in its 1994 report, that unstimulated whole saliva flow rate and minor salivary gland biopsy are two of the most
valuable diagnostic tests. Neither involves either exposure to X-rays or scintigraphy.

Mandel (1990) has noted that salivary function changes, in addition to a lowered secretion rate include raised Na\(^+\) and Cl\(^-\) but lowered PO\(_4\)\(^-\), raised lactoferrin, raised beta\(_2\) microglobulin, raised kallikrein concentrations and a 20-fold elevation in the concentration of phospholipids. Parotid gland lysozyme was also found to be raised in primary but not in secondary Sjögren's syndrome. Such changes could be useful as screening tests that could indicate whether labial gland biopsy or other tests were indicated but perhaps more important, for monitoring disease progress.

**Table 5.2** Typical figures for important constituents of saliva

<table>
<thead>
<tr>
<th>Substance</th>
<th>Unstimulated</th>
<th>Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± s. d.</td>
<td>Range</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>1.4-6.4</td>
<td>2.8</td>
</tr>
<tr>
<td>IgA (mg/L)</td>
<td>194.0</td>
<td></td>
</tr>
<tr>
<td>IgG (mg/L)</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>IgM (mg/L)</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Amylase (g/L)</td>
<td>0.38 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Lysozyme (mg/L)</td>
<td></td>
<td>108.9 ± 12.9</td>
</tr>
<tr>
<td>Carbonic anhydrase (K/L)</td>
<td>2100</td>
<td></td>
</tr>
<tr>
<td>Histamine (mg/L)</td>
<td>0.15</td>
<td>0.11-0.18</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>0.55±</td>
<td>0.048</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>3.22 ± 2.5</td>
<td>2.33-12.5</td>
</tr>
<tr>
<td>Creatinine (mg/L)</td>
<td>0.09</td>
<td>0.05-0.18</td>
</tr>
<tr>
<td>Cholesterol (mg/L)</td>
<td>0.2</td>
<td>0.07-1.3</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>6.2 ± 0.46</td>
<td>26.4 ± 11.8</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>21.6 ± 1.2</td>
<td>19.7 ± 3.9</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.56 ± 0.06</td>
<td>1.48 ± 0.04</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.21 ± 0.01</td>
<td>0.15 ± 0.04</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>17.4 ± 1.4</td>
<td>29.0 ± 8.8</td>
</tr>
<tr>
<td>Iodide (microm/L)</td>
<td>0.8</td>
<td>0-3</td>
</tr>
<tr>
<td>Fluoride (microm/L)</td>
<td>15 ± 0.68</td>
<td>0.5-3</td>
</tr>
</tbody>
</table>

**Cystic fibrosis**

Although all exocrine gland function is affected the clinical effects on salivary gland function are minimal, but there are significant changes in salivary composition. In particular, there are dramatic elevations in salivary protein and Ca\(^{2+}\) concentrations. The complexing of these substances leads to obvious turbidity of the saliva. This is such as to obstruct the excretory ducts of the minor salivary glands. Their greatly depressed secretion rate can be measured in the accessible labial glands with a capillary tube.
Hormone monitoring

Lipid-soluble, unconjugated steroids pass readily into saliva and their concentrations are proportional to the concentrations of free, unbound steroids in plasma as discussed by Ferguson (1987). Read (1993) has discussed the current status of salivary oestrogen and androgen measurements. An informative light on the limitations of salivary hormone measurements is cast by the problems of salivary dehydroepiandrosterone sulphate (DHA-S) assay. The salivary concentration of this hormone is only about 0.1% of that in plasma and is a poor predictor of plasma levels in an individual or a particular plasma sample. The inconsistencies arise from the fact that the concentration in parotid fluid is particularly low. Most salivary DHA-S probably therefore comes from blood in gingival exudate. The fall in DHS-S concentrations with high salivary flow rates helps to confirm this possibility. If this is the case, concentrations of DHA-S in saliva depend largely on the degree of contamination and as has been shown are affected by the oral conditions in the person being tested and the method of saliva collection.

Read (1933) concluded that salivary assays for testosterone in the male, androstenedione and oestriol in particular were valuable but considered that the value of salivary testosterone and oestradiol in the female remained unproven.

Ellison (1993) has considered certain technical aspects of salivary progesterone assay and their interpretation, and reviewed the utility of these assays for clinical purposes, particularly for the diagnosis and treatment of infertility. Salivary progesterone levels are valid indicators of plasma levels and Ellison (1993) concluded that their assay was particularly valuable because of the ease of obtaining serial samples from the same individual. On a shorter time scale, salivary monitoring could provide samples at short intervals for characterization of pulsatile progesterone patterns without the inconvenience and expense of hospitalization. The ability to adapt salivary progesterone monitoring under field conditions also made possible basic research on a wide scale into human reproductive biology. Ellison's (1993) concerns were the need for standardized laboratory procedures, methods of data reduction and analysis, recognized reference ranges and statistics on diagnostic efficiency. Further the low absolute levels of steroids in saliva placed a premium on an unusually high level of quality control in the laboratory.

Testosterone is a hormone that may additionally affect social behaviour. Assay of testosterone in saliva provides a valuable method for field studies. Dabbs (1993) has summarized the preliminary findings on differences in salivary testosterone levels both between and within individuals. Studies on individual differences are being carried in relation to violent and anti-social behaviour. Studies on changing testosterone levels are being carried out on winning sports contests, winning non-athletic events, winning political contests, 'winning' games of sex, and vicarious winning (sports spectators). Broadly speaking, it appeared that salivary testosterone levels fell in losers and were unchanged or rose in winners according to the importance of the victory. While animal studies confirmed elevations of testosterone with real or anticipated sexual activity there were considerable difficulties in obtaining samples at appropriate times in humans. However, it appeared that testosterone levels were higher on evenings when there was sexual activity, particularly in females, and low in its absence. Studies on salivary testosterone levels under conditions of abuse, depression and suicide were also in progress.
Salivary monitoring of viral antigens and antibodies

Viral hepatitis

In view of the hazard to surgeons, a simple method of detecting carriers of hepatitis viruses has obvious benefits.

The presence of hepatitis B antigen in saliva was demonstrated by Broderson et al (1974). Shikata et al (1985) were able to detect the surface antigen (HBSAg) and the core antigen in hepatocytes but could not detect either in parotid gland parenchymal cells. However, in the patient with the highest serum titre of HBSAg immunoreactivity was detected in the vascular wall and luminal fluid of the parotid gland. Piecentini et al (1993) have reported high sensitivity and specificity in the diagnosis of hepatitis A, B and C using the OraSure collecting system, and that the samples had titres of antibodies to viral hepatitis were similar to those of the serum.

HIV infection

Malamud (1992) has made a strong plea for use of saliva as a diagnostic fluid for the detection of antibodies to HIV among other purposes. For detection of carriage of antibodies to HIV, saliva testing as a simple non-invasive method presents enormous advantages. It removes the risk of needle-stick injuries and the emotional connotations of blood sampling in this alarming disease. Salivary sampling has special advantages when investigating children because of the great ease of collection. Archibald et al (1993) have described the practical applications for saliva testing for perinatal HIV diagnosis. Only a minority of infants born to HIV-positive mothers develop HIV infection, but in the neonatal period, usually carry passively transferred antibodies to HIV from the mother. However, it is believed that IgA and IgM antibodies do not cross the placenta. To assess the value of an IgA-specific Western blot assay, Archibald et al (1993) collected blood and saliva from 95 infants and children born to HIV-infected women. Saliva samples from infants were collected by gentle aspiration from the buccal sulcus. The total sensitivity of the salivary assay for detecting antibodies to HIV gp160 antigens was 50% of infants under 12 months old and 97.3% for infants over 12 months. The earliest age for detection of serum IgA antibodies to HIV is believed to be two months. Salivary IgA antibodies were detected by Archibald et al (1993) in an infected infant at six months but had been negative at four months.

Reliable salivary detection of HIV infection in the immediate neonatal period awaits more sensitive methods. However, if these can be found, saliva sampling for antibodies to HIV, particularly for infants and children, is a potentially valuable method. Saliva collection does not require skilled personnel, avoids the need for repeated venepunctures and is ideal for studies in developing countries.

Drug Monitoring in Saliva

Jusko and Milsap (1993) have discussed the pharmacokinetics of drug distribution in saliva. They showed that the primary properties of a drug determining its entry into saliva were molecular size, lipid solubility, pKₐ, and protein binding. However, salivary flow rates, the time of sampling, and disease states which altered saliva composition could affect the
Haeckel (1993) has summarized some of the reasons for the failure to use saliva to any great extent for therapeutic drug monitoring as follows:

--> Blood has to be sampled anyhow for other electrolytes.
--> There are technical difficulties with sampling saliva.
--> There are existing difficulties with the interpretation of salivary drug concentrations.

The remaining applications for saliva sampling were therefore:

--> When sampling at home is required.
--> Special cases where the sample is taken only for the monitoring of a particular drug.
--> Circumstances where the sample volume is critical, as for example in newborns, affect the results.

Nevertheless, if a constant saliva/plasma ratio can be established, use of saliva for therapeutic drug monitoring becomes a clinically useful possibility and Siegel (1993) has pointed out that the saliva/plasma ratios for at least 170 drugs have been established experimentally.

Drugs which can be monitored in saliva include digitalis, phenytoin, primidone, ethosuximide, carbamazepine, theophylline, caffeine, lithium, methadone, cyclosporin, marijuana, cocaine and alcohol.

A related use for salivary drug monitoring is for detection of drugs of abuse as described by Cone (1993) who reviewed the findings for alcohol, amphetamines, barbiturates, benzodiazepines, caffeine, cocaine, inhalants such as general anaesthetic agents as well as solvents, LSD, marijuana, opioids, phencyclidine and tobacco.

Xerostomia

Even in the absence of parenchymal salivary gland disease, function can be abnormal and result in xerostomia. However, it should not be assumed that ageing itself causes deterioration of salivary gland function. Several studies have been carried out and have yielded somewhat conflicting results. The most recent study (Ship et al, 1991) confirms at least one of the earlier studies that normal postmenopausal women, the main group thought to be at risk, have no deterioration of salivary gland function. However, postmenopausal women have the highest incidence of Sjögren's syndrome and are also the group who most frequently complain of symptoms such as sore mouth or even of dry mouth, though the later may not be confirmed by objective testing.

Aetiology

In assessing the cause of depressed salivary secretion a careful drug history is essential. Causes of xerostomia include the following:
Depression and chronic anxiety states.

Dehydration (fluid deprivation or excessive loss).

Salivary gland disease. See Table 5.2.
- Sjögren's syndrome and benign lymphoepithelial lesion (Chapter 4)
- radiation damage (Chapter 4)
- graft-versus-host disease (Chapter 4)
- sarcoidosis (Chapter 4)
- HIV infection
- iron and other infiltrations (Chapter 3)
- amyloidosis (Chapter 3)
- type V hyperlipoproteinaemia.

Depression and anxiety states

The rate of salivary secretion was measured in 42 untreated depressed patients by Busfield and Wechsler (1961a) who, in confirmation of the results obtained by earlier workers, found it to be decreased in comparison with non-depressed hospital patients and healthy controls. No correlation was found between the degree of xerostomia and the assessed severity of depression, nor was there any difference found in secretion rates in a later study by Busfield and Wechsler (1961b), between the different categories of depression or between those who complained of dry mouth and those who did not.

Chronic fatigue syndrome (myalgic encephalomyelitis)

In a survey on several hundred patients with chronic fatigue syndrome ('myalgic encephalomyelitis'), Komoroff and Buchwald (1991) noted that 30-40% complained of dry mouth. Whether or not this is related to the widely held view that this syndrome is a form of depression is also speculative. The question whether or not it has an organic basis also remains controversial, but the many suggested causes seem unlikely to have any organic effect on the salivary glands. However, this does not exclude the possibility of coincidental disease, especially as some organic disorders, such as the connective-tissue diseases in their early stages, can also give rise to vague and varied symptoms similar to those of chronic fatigue syndrome. Investigation may therefore be indicated.

Anxiety states may also be associated with significant sympathetic overactivity and drying of the mouth. When this affects actors or other public speakers, it can be a troublesome occupational hazard; in such patients, a beta-blocking agent such as oxprenolol may possibly be helpful.

The fact that xerostomia is associated with sympathetic overactivity, can be caused by sympathomimetic drugs and may be relieved by beta-blockers strongly suggests that the sympathetic supply to the salivary glands is inhibitory in humans. Nevertheless, Garrett (1987), in addition to the points made earlier in this section, strongly denies that sympathetic inhibitory fibres exist but that anxiety-induced xerostomia is due to central inhibition from higher centres. These in turn act on the salivary centres and thereby suppress reflex activity. The clinical implications of these findings are as yet unclear, especially as Garrett (1987) has emphasized that wide variations exist in the neuroeffector arrangements and in the cellular
responses of different glands from different species.

**Dehydration**

Drying of the mouth is an inevitable consequence of dehydration. It can therefore result from such causes as haemorrhage, loss of other body fluids secondary to diarrhoea or chronic vomiting, polyuria secondary to diabetes mellitus, hypovolaemia from any cause, restricted fluid intake or overdose of diuretics. As mentioned in Chapter 4, Raad *et al* (1990) found that acute bacterial sialadenitis was secondary causes such as these in approximately 50% of their patients.

**Drug-induced xerostomia**

Tricyclic antidepressants and phenothiazine neuroleptics are among the most troublesome as they have particularly strong antimuscarinic effects, are generally used over long periods and as a result of such side-effects as these, are disliked by most patients. Ganglion-blocking drugs are obsolete in the routine management of hypertension, and modern antihypertensives are considerably more selective in their action.

However, by simplistic analogies between quite different groups of drugs, which happen to be used for similar medical indications, widespread misunderstandings persist about the effects of different drugs on salivary gland function but few objective trials confirm these assertions. For example, antihypertensive drugs in general, are frequently said to cause xerostomia, but beta-blocking drugs which are currently among the most widely used for this purpose, have not been shown to decrease salivary secretion. Moreover, by blocking sympathetic activity, they are more likely to increase secretion and, as mentioned earlier, may be used beneficially by actors for example, whose mouths dry up on stage. Similarly, the commonly used benzodiazepines ('minor tranquilizers') do not cause dry mouth and may even relieve anxiety-induced xerostomia. By contrast, neuroleptic drugs (formerly termed 'major tranquilizers'), particularly the phenothiazines, have strong antimuscarinic side-effects and cause significant drying of the mouth.

In practical terms, the chief effects of prolonged xerostomia are the distressing symptom itself and the promotion of oral infections as discussed below.

**HIV infection**

The varied effects of HIV infection on the salivary glands are discussed in Chapter 4. It needs only to be noted here in that deterioration of function appears to have no consistent relationship with lymphoproliferative lesions of the glands in the various reports. By contrast, studies have shown progressive impairment of salivary flow rates associated with HIV infection in patients apparently without over salivary gland disease.

As yet, it is as difficult to correlate these apparently contradictory findings as to evaluate the effect of benign lymphoepithelial lesion (Chapter 8) on salivary function, despite their having the same microscopic appearances as Sjögren's syndrome.
Type V hyperlipoproteinaemia

Xerostomia, sometimes associated with parotid swelling, is sometimes a major complaint in type V hyperlipoproteinaemia. However, the pathogenesis is unclear. According to Reinertstein et al (1980) labial gland biopsies have shown no abnormality but salivary gland scintigraphy suggests that focal inflammatory, infiltrative or obstructive lesions may be present.

Clinical features

It is important to appreciate that, as confirmed by Fox (1987), Sreebny et al (1988) and others, patients with impaired salivary flow rates frequently make no spontaneous complaint of dry mouth and may not even admit to it if asked. However, they may admit to difficulties with eating dry foods unless taken with fluid. By contrast, patients who complain of dry mouth are not uncommonly found to have normal flow rates. In extreme cases dryness of the oral mucosa is obvious (Fig. 5.2), but even when the flow rate is significantly diminished, the mucosa usually appears moist. In such cases, diminished salivary flow is indicated by absence of pooling of saliva in the floor of the mouth and frequently by salivary froth adhering patchily to the mucosa (Fig. 5.3).

In severe cases, xerostomia can be recognized even before examination by the clicking quality of the patient's speech as a result of the tongue adhering to the palate.

Much also depends on the rest of the clinical picture. A patient complaining of dryness of the mouth and who has long-standing rheumatoid arthritis or a history of irradiation of the oral cavity, or is on tricyclic antidepressant treatment, is unlikely to need the complaint to be confirmed by testing.

Oral changes suggestive of a dry mouth are the onset of rapid dental decay which often affects unusual sites such as the lower anterior teeth (Fig. 5.), adherence of food debris to the teeth, or soreness and redness of the oral mucosa due to Candida albicans infection (Fig. 5.5). In extreme cases, the oral mucosa appears wrinkled and parchment-like, or rarely, sores may be seen on the palate or elsewhere (Fig. 5.6). Changes in the oral flora secondary to drying can also lead to complaints of unpleasant taste sensation or halitosis. A feature characteristic of Sjögren's syndrome is that the tongue becomes red, partially depapillated and lobulated. Occasionally the onset of suppurative parotitis is the first indication of impaired salivation.

Because of the erratic correlation between the complaint of dryness of the mouth with impaired salivation, objective confirmation of decreased flow rates may be necessary. It is particularly required in Sjögren's syndrome where a variety of abnormalities (Chapter 4) may be present but their association with the disease is inconstant. In the case of salivary lymphoepithelial lesion, flow rates are unlikely to be measured, because the disease is usually only recognized after parotidectomy.

It is also important to remember that dryness of the mouth is frequently associated with poor lacrimal gland function, particularly in Sjögren's syndrome. Conjunctivitis is occasionally obvious, but early keratoconjunctivitis sicca is asymptomatic.
Management

The distressing nature of this complaint should not be underestimated as it so frequently is by surgeons. Considerable effort to make the patients comfortable and their meals more pleasant is justified.

The two requirements are relief of the symptoms and control of the complications. The patient should not be told, as sometimes happens, to suck acid drops. The sugar and acid content of these sweets will quickly lead to destruction of any remaining teeth and probably also help to promote other infections.

Patients should take plenty of fluid in the form of frequent sips of water (or as Seifert et al (1986) suggest, low-alcohol beer), particularly with meals. Sugar-free chewing-gum is frequently also helpful as mastication reflexly increases salivary flow.

Artificial salivary are also beneficial. However, these preparations inevitably lack the same degree of lubricating and other essential properties of normal saliva and, in any case, cannot be used in quantities comparable to natural flow rates. If one assumes, for simplicity, an average flow rate of normal saliva, of 2 mL/min this represents 1.44 litres of saliva over a period of 12 h. The use of artificial salivas in such quantities as great as this is hardly feasible, but patients should be encouraged to use them as freely as possible.

Even if artificial salivas are used conscientiously and in as large quantities as possible, there is still unpleasantly impaired and abnormal taste sensation and frequently as a consequence, poor appetite.

Cholinergic drugs, such as pilocarpine, have been reported to be of value but functional salivary tissue must be present, and their other effects, particularly diarrhoea, may limit their usefulness.

Control of oral infection is important. Standing teeth rapidly decay and periodontal infection is accelerated unless stringent precautions are taken. If not, extraction of teeth becomes necessary and dentures are frequently then difficult to manage. Extractions are particularly hazardous after radiation damage to the tissues, as the risk of radiation-associated osteomyelitis is high. Meticulous preventive dental care is therefore essential; this includes attention to the diet, rigorous oral hygiene measures and application of fluorides.

In addition to dental decay, the mucosal flora changes and Candida albicans or staphylococci frequently proliferate. Candidosis should be controlled with an antifungal preparation such as amphotericin or nystatin suspension. Alternatively, antifungal imidazoles such as ketoconazole suspensions or miconazole gel may be more effective and may also help to control associated bacterial infections. There preparations are more suitable than tablets which may not dissolve, and the patient should be told to hold them in the mouth for as long as possible to achieve the maximal effect.

The changes in the oral flora are probably a major cause of the abnormal taste sensations in this condition. Lack of parotid salivary flow also increases the risk of bacterial (ascending) parotitis. This risk should also be lessened by maintenance of high standards of
oral hygiene.

Nevertheless, as mentioned earlier, the possibility of asymptomatic keratoconjunctivitis sicca should be excluded. If neglected it can lead to irreparable damage to sight. Paradoxically therefore, ocular examination may be the most important aspect of the care of a patient with xerostomia. Even if salivary gland function is normal, slit-lamp examination may be desirable in the case of several of the diseases listed earlier.

**Sialorrhoea**

**Table 5.3 Causes of ptyalism**

Local reflexes
- Painful oral infections
- Oral wounds
- Dental procedures
- New dentures

Systemic
- Nausea
- Acid regurgitation (reflux oesophagitis)

Toxic
- Iodine
- Heavy-metal poisoning

False ptyalism
- Psychogenic
- Bell's palsy
- Parkinson's disease
- Stroke
- Cerebral palsy.

A few drugs or painful conditions in the mouth may increase salivation, but this is not a significant complaint as any excess of saliva can normally be swallowed. 'False ptyalism' is more common and is either delusional (a disturbed patient may suddenly become alarmed at 'water' or 'too much saliva' continually appearing in the mouth) or due to faulty neuromuscular control that leads to drooling despite normal salivary flow (Table 5.3).

If lip function and swallowing are normal, the complaint of hypersalivation ('too much saliva' or 'water coming into the mouth') is essentially neurotic.

Drooling is not usually due to excessive salivation but either to difficulty in swallowing or abnormal lip function; this is well shown in Parkinson's disease where drooling may persist even when antimuscarinic drugs (orphenadrine, benztropine, benzhexol or procyclidine) are being given and salivary secretion is impaired. Inadequate lip function and drooling is also common in mental defectives.

The surgical management of drooling is discussed in Chapter 9. Though hardly relevant in the present context, the importance of defective deglutition in severe sialorrhoea is exemplified by the sign traditionally known as 'foaming at the mouth', in the later stage of
rabies. Severe dysphagia results from brain-stem dysfunction and there is also excessive salivation due to autonomic overactivity. The defect in deglutition frequently leads to so-called 'hydrophobia', in which any attempt to swallow liquids, leads to violent, painful and terrifying contractions of the pharyngeal, laryngeal accessory respiratory muscles and diaphragm. Survival after the onset of such symptoms is usually less than a week. Rabies virus spreads centrifugally to the salivary glands from the central nervous system and is present in the saliva. It is the main vehicle for transmission of the infection from animals, but spread by this means from a patient to a health worker does not appear to have been reported.

**Frey's Syndrome**

Frey's syndrome (gustatory sweating, auriculotemporal syndrome) usually results from damage to the innervation of the salivary glands during parotidectomy and is probably caused by faulty regeneration of autonomic fibres secondary to the injury.

Clinically, Frey's syndrome is characterized by sweating, warmth and redness of the face as a consequence of autonomic stimulation of salivation by the smell or taste of food. The sweating can be demonstrated by coating the side of the face with starch, which turns blue on exposure to iodine in the sweat (Fig. 5.7).

Once established, Frey's syndrome is difficult to treat. Application of ointments, containing anticholinergic drugs, to the face to inhibit sweating, or commercial antiperspirants (usually based on astringents such as aluminium chloride) should be tried in the first instance. Denervation by tympanic neurectomy or auriculotemporal nerve avulsion has been advocated when simpler measures fail.

**Note**

1. Lucie Frey, Polish physician (1898-1944), murdered by the Nazis.
Chapter 6: Adenomas of salivary glands

One of the many difficulties of salivary gland surgery is the great variety of neoplasms that can form in the salivary gland tissues, and confusion has been caused by the changes in terminology. The World Health Organization classification of Thackray and Sobin (WHO, 1972) is shown in Table 6.1. Though this classification has been of great value and is still widely used, it has inevitably been overtaken by the recognition of new tumour entities. To take these into account, the WHO Histological Typing of Salivary Gland Tumours (Seifert, 1991) has been devised and is shown in Table 6.2.

Table 6.1 Histological typing of salivary gland tumours (Thackray and Sobin, 1972).

I. Epithelial tumours
   A. Adenomas
      1. Pleomorphic adenoma (mixed tumour)
      2. Monomorphic adenoma
         (a) Adenolymphoma (Warthin's tumour)
         (b) Oxyphilic adenoma
         (c) Other types
   B. Mucoepidermoid tumour
   C. Acinic cell tumour
   D. Carcinomas
      1. Adenoid cystic carcinoma
      2. Adenocarcinoma
      3. Squamous cell carcinoma
      4. Undifferentiated carcinoma
      5. Carcinoma in pleomorphic adenoma (malignant mixed tumour)

II. Non-epithelial tumours

III. Unclassified tumours

IV. Allied conditions
   A. Benign lymphoepithelial lesion
   B. Sialosis
   C. Oncocytosis.

Inevitably, such a classification involves some compromises and for practical clinical reasons have not rigidly followed precisely the same sequence in this text. For example, cysts have been discussed in Chapter 3 and since they may be difficult to distinguish, tubular-trabecular adenomas are discussed with the canalicular type. It also seems more appropriate to discuss together benign lymphoepithelial lesion and lymphomas (Chapter 8).

The structure of this chapter is thus:

➤ Pleomorphic adenomas including myoepithelioma.
➤ Monomorphic adenoma including Warthin's tumour and oncocytoma.
➤ Tumour-like lesions.
Table 6.2 Histopathological classification of salivary gland tumours (Seifert, 1991)

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumour Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Adenomas</td>
<td>Pleomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td>Myoepithelioma (myoepithelial adenoma)</td>
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<tr>
<td></td>
<td>Basal cell adenoma</td>
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<tr>
<td></td>
<td>Warthin's tumour (adenolymphoma)</td>
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<tr>
<td></td>
<td>Oncocytoma (oncocytic adenoma)</td>
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<td></td>
<td>Canalicular adenoma</td>
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<td></td>
<td>Sebaceous adenoma</td>
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<tr>
<td></td>
<td>Ductal papilloma</td>
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<td></td>
<td>Inverted ductal papilloma</td>
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<tr>
<td></td>
<td>Intraductal papilloma</td>
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<td></td>
<td>Sialadenoma papilliferum</td>
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<tr>
<td></td>
<td>Cystadenoma</td>
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<tr>
<td></td>
<td>Papillary cystadenoma</td>
</tr>
<tr>
<td></td>
<td>Mucinous cystadenoma</td>
</tr>
<tr>
<td>II. Carcinomas</td>
<td>Acinic cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Mucoepidermoid carcinoma</td>
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<tr>
<td></td>
<td>Adenoid cystic carcinoma</td>
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<tr>
<td></td>
<td>Polymorphous low-grade (terminal duct) adenocarcinoma</td>
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<td></td>
<td>Epithelial-myoepithelial carcinoma</td>
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<td></td>
<td>Basal cell adenocarcinoma</td>
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<tr>
<td></td>
<td>Sebaceous carcinoma</td>
</tr>
<tr>
<td></td>
<td>Papillary cystadenocarcinoma</td>
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<tr>
<td></td>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Oncocytic carcinoma</td>
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<tr>
<td></td>
<td>Salivary duct carcinoma</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma (not otherwise specified)</td>
</tr>
<tr>
<td></td>
<td>Malignant myoepithelioma (myoepithelial carcinoma)</td>
</tr>
<tr>
<td></td>
<td>Carcinoma in pleomorphic adenoma (malignant mixed tumour)</td>
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Pleomorphic Adenoma

Pleomorphic adenoma is by far the most common salivary gland tumour, and though benign, presents peculiar, but well-known problems both in terms of histological diagnosis and management (see Diagnostic flow chart, p 83). The diagnostic difficulties are rare but in brief, are those of determining whether there has been malignant change and whether such changes are entirely within the tumour margins. Rarely there is the problem of an obviously invasive tumour despite being cytologically benign (Chapter 7).

By contrast, the surgical difficulties (Chapter 9) are considerable in the case of parotid gland tumours because of the frequent lack of adequate capsulation and the proximity of vital structures. These difficulties can be greatly increased in the case of recurrences, particularly if there has been previous irradiation.

Clinical aspects

The mean age at presentation of pleomorphic adenomas of the parotid glands is 46 years, but the age range is from 8 years to > 80 years. Overall, there is a slight female predominance (1.4 to 1) which becomes increasingly great after the third decade. In the submandibular glands, there is a greater female predominance (1.7 to 1) and the peak age of incidence is in the sixth decade. However, there appears to be no regular pattern of distribution according to age and sex.

The great majority (78%) of pleomorphic adenomas are found in the parotid glands where they form slow-growing, usually painless, firm, swellings which are not attached to the overlying skin. Any impairment of facial nerve function, pain or ulceration of the overlying skin strongly suggests malignant disease. However, pain is occasionally reported in benign tumours.

Eighty per cent of parotid pleomorphic adenomas are within the superficial lobe and 20% arise either within the deep lobe or involve it by direct growth from the superficial lobe. Clinically, deep-lobe tumours give rise to a parapharyngeal mass, displacing the soft palate and tonsil medially. This may cause a change in character of the voice but usually its onset is so subtle as to evade recognition until the diagnosis has been made. Difficulty in swallowing is unusual and most deep-lobe tumours are incidental findings at consultations for other complaints. These tumours have frequently reached a large size (for example, 5-10 cm) at this stage. Management is dictated by the lobe to which the tumour is confined, and its size. It is important not to assume that a parapharyngeal tumour has arisen from a minor pharyngeal salivary gland.

Rarely, a pleomorphic adenoma forms in accessory parotid tissue along the line of the duct and then may only be visible when the mouth is opened and the tumour is pushed outward by the forward movement of the coronoid process of the mandible.

As to other salivary glands, 11% of all pleomorphic adenomas are found in the submandibular glands and a similar proportion is found in minor salivary glands. In the minor glands, the majority (60%) of pleomorphic adenomas are found in the palate, the next most common sites are the lips (22%) and the cheeks (10%). They are also occasionally found in
other sites such as the tongue, retromolar fossa, pharynx or tonsil. By contrast, these tumours are exceedingly rare in the sublingual glands, but are occasionally found in sites in the airways extending from the nasal cavity to the bronchi, the middle ear and external auditory meatus and in the lacrimal glands.

The clinical features of pleomorphic adenomas in the other major or minor salivary glands do not differ significantly from those in the parotids. However, pleomorphic adenomas within the mouth may have a readily palpable, bosselated surface and bluish areas may be discernible through the mucosa. In addition, these tumours, like any others in the mouth and particularly those in the palate, can become ulcerated by friction. The firmness of these tumours varies with the nature and amount of the stromal component and thus ranges from soft (in the case of the more mucinous tumours) to hard (in the case of tumours with an extensive chondroid or collagenous component).

The size of salivary gland tumours varies greatly. Those within the mouth are likely to be noticed when they are only 5-10 mm across while those in the parotid glands are more likely to be 2-5 cm in diameter or even larger when arising in the deep lobe. Giant pleomorphic adenomas of 20-30 cm diameter are rarely seen today. Probably the largest on record was a tumour weighing 27 kg, that had been present for about 30 years. Chang and Lee (1985) have shown an example of one 21 cm in diameter and appearing larger than the rest of the man's head. Among cases referred to us was one which extended down to the clavicle and weighed 775 g.

Occasionally, pleomorphic adenomas are associated with another salivary gland tumour, though less frequently than Warthin's tumours. The other tumour may be synchronous or metachronous, in the same gland or on the opposite side.

Microscopy

The variety of appearances is remarkable and it may be helpful, as discussed later, to categorize the main types of appearance according to the classification of Seifert et al (1986). The essential components are:

- Capsule (complete or incomplete).
- Epithelial cells in a variety of configurations.
- Myoepithelial cells.
- Stroma which may be fibrocollagenous, myxoid, chondroid or myxochondroid, in varying proportions, but which forms the bulk of the tumour in the majority of cases.

Capsule

Pleomorphic adenomas have a capsule which ranges from thick and fibrous to complete absence around at least part of the tumour. The degree of encapsulation and the ability of these tumours to extend through the capsule, is of such practical importance in their
management that it is discussed later in that context.

Epithelium

Duct-like structures are common but acini are rare. The epithelial cells may be columnar, cuboidal, squamous or flattened and in sheets of greater or lesser extent but interspersed by stromal elements (Figs 6.1 and 6.2). In some tumours, epithelium is scanty and stroma forms the bulk of the mass as discussed below.

In the ducts, the epithelium forms the lining cells (Figs 6.3 and 6.4) and sometimes, small darker myoepithelial cells can be seen as a distinct outer layer; some of the latter cells may have clear cytoplasm (Fig. 6.5). The ducts may be empty or contain eosinophilic colloid material, which may stain strongly with periodic acid-Schiff (PAS) reagent. Ducts are frequently small but may be so distended as to appear as microcysts, but gross cyst formation is rare. By contrast, duct-lining cells may form rosette-like structures, many of which lack a lumen. Occasionally these cells may produce mucus which may be distinguished chemically from the connective-tissue mucin of the stroma.

Squamous metaplasia with keratinization is common; the keratin may form whorls or microcysts or more irregular masses within the epithelium (Fig. 6.6). Very occasionally the epithelium may form goblet or mucous cells, which in association with the squamous epithelium can give an appearance with some resemblance to a mucoepidermoid carcinoma. Rarely, sebaceous tissue may be associated or there may be formation of epithelial giant cells (Fig. 6.7). Fat, a normal component of parotid tissue, may also be seen among the epithelial cells. This may be a particularly striking feature, even in minor salivary gland tumours, and in association with poor encapsulation, can give a misleading impression of invasion (Fig. 6.8).

A few clear cells are sometimes found and these may be in trabecular, thecal or ductular configurations (Fig. 6.9). In older tumours, the epithelium may undergo oncocytic change and, rarely, this can be so extensive as to mimic an oncocytoma (Fig. 6.10).

Myoepithelial cells and stroma

As noted earlier, myoepithelial cells are not reliably identifiable with routine stains. With haematoxylin and eosin, they are most often seen as small, darkly staining cells surrounding duct lining cells (Fig. 6.5), as sheets, thinly dispersed as fine strands (Fig. 6.11) or even isolated in mucoid material or merging with the cartilage-like cells in cartilaginous areas. In other situations they can be polygonal and plump, or spindle-shaped with fibrillar cytoplasm and so resemble the cells of a leiomyoma. Their most distinctive appearances are as hyaline cells, strongly resembling plasma cells, or as spindle cells which may so dominate the picture as occasionally to suggest a mesenchymal tumour. Such tumours are usually then termed 'myoepitheliomas' and rarely, these elongated, fusiform myoepithelial cells may show nuclear pallisading like that in a neurilemmoma (Fig. 6.12).

The basophil myxoid stroma of pleomorphic adenomas is one of its most characteristic features (Fig. 6.13). It can form the major part of the tumour, when epithelial components can be difficult to find, and can bulge into the normal gland parenchyma without any capsule.
intervening. This material has similar staining characteristics to that of connective tissue glycosaminoglycans and is metachromatic with toluidine blue, but PAS-negative. With the latter stain therefore, the myoepithelial cells and their stellate form can be clearly seen, especially as their cytoplasm becomes more strongly PAS-positive in a mucoid matrix.

Hyaline material is another stromal component which may be interspersed among the epithelial cells (Fig. 6.14); it normally appears structureless but by diffracted light appears fibrillar and arranged in stellate fashion or in sheaves (Fig. 6.15). Occasionally hyaline material is so abundant as to put apart the darkly staining epithelial cells to give a cribriform or cylindromatous pattern which can readily be mistaken for an adenoid cystic carcinoma (Fig. 6.16). It is important to recognize this appearance as artefactual as it is of no prognostic importance.

The cartilage of pleomorphic adenomas, though often termed 'pseudo-cartilage' does not appear distinguishable in any way from true cartilage. Indeed, it has been shown by immunocytochemistry to contain the proteoglycan, keratan sulphate, a characteristic of true cartilage (Fig. 6.17). Very occasionally, it is the major component with the result that the whole tumour when cut across, is crisp, firm, glistening and translucent with only strands of soft tissue interspersed among the cartilaginous masses. The cartilage may rarely even contain true bone with fatty marrow spaces, but calcification is more common, both in cartilage and in hyaline stromal material (Fig. 6.18). Bone is occasionally also seen in the absence of cartilage, as a result of stromal metaplasia (Fig. 6.19). Calcifications or bone formation, which are unlikely to be seen in any other salivary gland tumour, may occasionally be prominent in radiographs and when seen in a salivary gland or a parapharyngeal mass, strongly suggests that the tumour is a pleomorphic adenoma.

Elastic tissue can be found in greater or lesser amounts in most pleomorphic adenomas. It is refractile, stains bright red with haematoxylin and eosin, and may be conspicuous in globular masses or broad irregular bands in some tumours (Fig. 6.20). It may also be seen in long-standing tumours as irregular rings as a residue of the basement membrane region of ducts which have degenerated and disappeared.

Progressive elastosis and fibrosis can eventually lead after many years, to the tumour becoming predominantly sclerotic (Fig. 6.21). This may be dismissed as mere scarring, but malignant change may be associated and examination of such tumours should be particularly thorough, despite their superficially bland appearance.

**Histological subclassifications**

Subclassifications have not been widely shown as yet to provide any precise guide to the behaviour of pleomorphic adenomas. However they provide a useful basis for description and an indication of the main types of variants that are seen and their relative frequency. The main subtypes described by Seifert et al (1986) are as follows.

**Type 1.** Comprises 30% of cases. Mucoid stroma forms 30-50% of the tumour and the cellular component consists of duct, epidermoid and myoepithelial cells, in solid and tubular or cystic arrangements.
Types 2(a) to 2(e). Comprise 55% of cases. Mucoid stroma forms 80% of the tumour; the cellular components are as in Type 1. In type 2(a) (37.5% of cases) the stroma is mucoid; in type 2(b) (2.5%) it is chondroid; in type 2(c) (5.0%) it is mucochondroid; in type 2(d) (0.5%) it is fascicular; in type 2(e) (8.5%) it is hyaline-fibrous.

Type 3. Comprises 9% of cases. Stroma forms only 20-30% of the material but this and the epithelial components do not otherwise differ from subtypes 1 and 2.

Type 4. Comprises 6.5% of cases. This differs from subtype 3 only in so far as there is some monomorphic differentiation in the epithelial component.

According to this analysis therefore, the stroma forms 80% of the tumour in > 50% of cases, and this has important implications for management. When the stroma is mucoid, spillage of tumour at operation is a strong possibility if handling is unsympathetic and, as might be expected, Seifert et al (1986) report that recurrence is more frequent with stroma-rich (subtype 2) tumours. Otherwise, these subtypes are not known for certain to have any constant relationship with prognosis. However, it seems likely that highly cellular tumours are more likely to undergo malignant change and Seifert et al (1986) report that almost 50% of carcinomas in pleomorphic adenomas develop in the cell-rich variant (subtypes 3 and 4).

Palatal tumours, incidentally, are rarely mucoid.

**Crystalline and other inclusions**

Tyrosine crystals are a recognized but rare finding in pleomorphic adenomas, particularly in those affecting Blacks. The crystals are recognizable by their refractile appearance and daisy head configuration and by their reddish pink staining with Mayer's haemalum and tartrazine (Fig. 6.22). These crystals are uncommon even though salivary tissue concentrates tyrosine.

Rarely, pleomorphic adenomas have been reported to contain large amounts of oxalates which formed dense basophilic crystals frequently arranged radially.

Corpora amylacea (Fig. 6.23) and amyloid are occasional findings. The amyloid may be a product of the tumour as in the case of basal cell carcinomas and other epithelial tumours and is unlikely to be secondary to systemic amyloid disease which rarely affects salivary glands (Chapter 4).

**Capsular integrity and implications for management**

Pleomorphic adenomas expand and grow in localized areas of proliferation and as a consequence have an irregular nodular form macroscopically and can also be seen, microscopically, as bulging or mushrooming into the capsule (Fig. 6.24). Nevertheless, these tumours are not multifocal as was at one time thought, and apparently isolated islands of tissue in an untreated tumour will be found, on deeper sectioning, to be outgrowths of the main mass although they may occasionally be joined to it by only a thin isthmus.
The capsule can vary considerably within the plane of one section and even when thick, may have tumour growing into it (Fig. 6.25) or penetrating it. In addition, clefts can form parallel with the surface (Fig. 6.26), just within the tumour and provide a false plane of cleavage which would leave behind a layer of tumour cells, if there were a mistaken attempt at enucleation. In yet other cases there may be no capsule separating the tumour from the surrounding gland (Figs 6.27 and 6.28).

The incomplete encapsulation of pleomorphic adenomas has been well documented by Patey and Thackray (1958), Batsakis (1986) among others and as illustrated here. Patey and Thackray (1958), in particular, established by serial sectioning of excision specimens that focal infiltration of the capsule was common and that subcapsular clefts just within the tumour borders provided false planes of cleavage. Whole organ sectioning of excised pleomorphic adenomas by Lam et al (1990) has also confirmed that all specimens had bare areas (absence of normal salivary tissues round the margins) and that in every case, the capsule was infiltrated by tumour. In a third of the cases, the capsule was incomplete and tumour was in direct contact with salivary tissue.

The integrity of the capsule can therefore vary considerably even within the plane of a single section and even when thick and fibrous, can have tumour growing into it (Fig. 6.24) or penetrating it (Fig. 6.25).

Management

In addition to incomplete encapsulation, the mucoid nature of many pleomorphic adenomas means that they can readily burst at operation, even with the most delicate handling, unless protected by the envelope of normal glandular tissue that parotidectomy provides.

As a result of this poor encapsulation of pleomorphic adenomas, attempts at enucleation have frequently resulted in recurrences because of the ability of residual tumour cells to continue to proliferate. Several points about the recurrence of these tumours are of great practical importance. First, it may take more than a decade for them to become apparent. Stevens and Hobsley (1982), for example, noted that in cases where secondary parotidectomy had had to be carried out for recurrences, these had sometimes appeared more than 20 years after operation. Claims of cures based on disease-free periods of up to 10 years may therefore be misleading.

Second, recurrences are typically multiple (Fig. 6.29) as shown by Patey and Thackray (1958) and that though they were frequently in the incision scar, recurrent nodules were often widely separated from each other. This multiplicity of recurrent tumour nodules clearly makes for great difficulty in management. If it is suspected early on that excision has been incomplete, it may be difficult to identify and remove minute nodules at re-operation; further recurrences therefore follow. If treatment is delayed until the recurrences are obvious, then their removal may be even more difficult. Clairmont et al (1977), for example, reviewed 53 patients referred to them for recurrences after attempted enucleations in other hospitals. In these patients the operation had become progressively more difficult and eight of them had further recurrences until in some cases the tumour formed a fixed bulky conglomerate, removal of which sometimes required resection of the facial nerve. In some cases, this
continued proliferation of tumour cells can result ultimately in a mass of innumerable tumour nodules in the neck and virtually insuperable operative difficulties.

Finally, as discussed later, the incidence of malignant change is greater in recurrent tumours.

In summary then, the major difficulties in the management of pleomorphic adenomas include:

➤ The incompleteness of the capsule makes attempts at enucleation likely to leave residual tumour cells.

➤ The ability of seeded tumour cells to proliferate outside the original margins and particularly in the incision scar, makes recurrence likely after incomplete excision. The ability of the tumour to regenerate in fibrous scar tissue may be a reflection of its low biological requirements.

➤ The long delay before some of these recurrences become apparent can give a false sense of security that may encourage dangerously conservative treatment.

➤ Most pleomorphic adenomas are in the parotid glands where radical treatment is difficult and threatens the integrity of the facial nerve.

➤ Recurrences are more difficult to treat than the original tumour. Attempts to eradicate recurrences, unless totally successful, can lead to further recurrences, which may necessitate resection of the facial nerve for their removal or may ultimately prove to be unmanageable.

➤ The incidence of malignant change is greater in recurrences and increases with each subsequent recurrence.

In short, pleomorphic adenomas have an unusually strong tendency to recur in the incision scar if opened at operation or if incompletely excised. These peculiarities of the behaviour of pleomorphic adenomas make it clear that, however, tempting the idea may be, enucleation is not an acceptable option. Enucleation is only possible when tumours are completely enclosed within a firm fibrous capsule. As already discussed, this rarely applies to pleomorphic adenomas and even at operation, there can be no certainty that an adequate capsule exists. These points cannot be emphasized too strongly because of continued recommendations and attempts to enucleate pleomorphic adenomas.

Another problem is that of deep-lobe parotid tumours and the possibility that they may have arisen in minor pharyngeal glands. However, as discussed earlier, whole-organ sectioning of parotidectomy specimens has shown that extensions of a pleomorphic adenoma may only be joined to the rest of the tumour by a thin neck. It is unwise, therefore, to assume that a deep-lobe tumour is anything other than a parotid gland tumour and therefore to attempt to remove it by a transpharyngeal approach. However, magnetic resonance imaging may
sometimes make it possible to distinguish minor parapharyngeal gland tumours from extensions of parotid gland tumours.

Parotidectomy, or wide excision of pleomorphic adenomas in other glands is therefore the only reliable method of preventing recurrences. The risk of damage to the facial nerve has to be faced, but in skilled hands the level of risk is low. In a series reported by Maynard (1988), of 156 pleomorphic adenomas (including 26 recurrent tumours), personally treated by parotidectomy, there was only a single case of permanent facial weakness. The completeness of these excisions is shown by the fact there was only a single local recurrence after a follow up period of 20 years. Earlier, Gleave et al (1979) reported permanent facial nerve paresis in 1.3% after removal of 369 pleomorphic adenomas though not all of these were parotidectomies.

Clearly, if it were possible to identify more manageable tumours with certainty preoperatively, the risks of parotidectomy might be avoided. However, by no means all hospitals have cytologists who can give firm diagnoses on salivary gland tumours. This is in no way a criticism of cytologists, but many will have difficulty in acquiring sufficient experience because of the low overall frequency of these tumours and their variety. Their problems are increased by the fact that there are at least nine main types of benign and 10 main types of malignant tumours, some of which cannot be distinguished purely cytologically.

Another difficulty with aspiration cytology is the presence, in some pleomorphic adenomas, of large areas of a uniform cell type resembling monomorphic adenomas. That consideration apart, needle biopsy could miss a limited area of malignant change in a pleomorphic adenoma.

It is also no longer so certain, as discussed by Hix and Aaron (1990), that the risk of seeding tumour cells into the needle path by fine-needle aspiration cytology is absent. This does not as yet appear to have been reported in the case of salivary gland tumours, but the possibility must be considered because of the slow growth of any implanted pleomorphic adenoma cells.

In the case of recurrent tumours, each case has to be decided on its own merits bearing in mind that multiple nodules are likely to be present. Such nodules are likely to be concentrated in the original incision scar but some may be more distant. Close examination of the area is therefore necessary and as wide an excision as possible should be carried out.

Truly solitary nodules of recurrent tumour are uncommon but should offer no special operative difficulties. However, a single recurrence may be difficult to remove safely, if overlying or attached by scar tissue to the facial nerve.

Radiotherapy

There seems to be no strong argument for irradiation, and few attempts seem to have been made to carry out controlled trials to test its efficacy. Zymbal (1938) implanted radium into the bed of 34 enucleated pleomorphic adenomas, but failed to prevent four recurrences after a short period of follow-up. By contrast, from 28 other tumours in which no radium was implanted, there was only a single recurrence. No other evidence appears to have been
produced to suggest that pleomorphic adenomas are radiosensitive. Further, it seems likely that irradiation may increase the risk of malignant change and its ability to induce salivary gland tumours is well known. Watkin and Hobsley (1986a) have noted malignant change in pleomorphic adenomas after radiotherapy and also reviewed earlier reports both of this complication and of the development of new salivary gland tumours after irradiation of adjacent sites (Watkin and Hobsley, 1986b).

In a tumour such as the pleomorphic adenoma which has a potential for spontaneous malignant change, the possibility that such a change could be induced or accelerated by radiotherapy seems inescapable. Further, radiotherapy if unsuccessful, makes later operative treatment more difficult as a result of subsequent fibrosis.

Despite these considerations, it has been suggested that irradiation may be of some value in specific cases, namely, ruptured pleomorphic adenomas with field contamination, tumours which have previously undergone open biopsy, and as an adjunct to surgical management of recurrent disease. Even though there is no clear evidence of any benefit, many surgeons (rightly or wrongly) still feel safer if postoperative radiotherapy is given to this subsection of patients, in the hope of delaying recurrences and ignore the risks that such measures involve. Nevertheless, the fact remains that there is little evidence as to the value of radiotherapy. The risk of inducing or accelerating malignant change seems to be strong and any putative benefits have also to be balanced against the surgical problems of trying to remove any recurrences from tissue made ischaemic and fibrotic by irradiation.

In summary, then, preoperative diagnosis of pleomorphic adenomas is unlikely to be completely reliable even when cytology services are available. Conventional biopsy of parotid gland tumours is also contraindicated and the attempt to enucleate pleomorphic adenomas brings with it a high risk of recurrences. These may not appear until more than 10 years later and can then be very difficult to manage. Many tumours are also predominantly myxoid and can burst at operation if not gently handled. Pleomorphic adenomas should therefore be removed by superficial or total conservative parotidectomy (or wide excision of other glands) at the first operation as discussed in Chapter 9 and radiotherapy as primary treatment is completely contraindicated.

If enucleation is attempted but histology confirms that the tumour is a pleomorphic adenoma and, particularly, if it suggests that encapsulation was incomplete, then the operation site must be excised as soon as possible and the tissue examined for microscopic recurrences.

**Dysplasia in pleomorphic adenomas (‘intracapsular carcinoma’)***

There are no reliable cellular indicators of the likelihood of malignant change. Mitoses are an occasional feature of benign tumours. High cellularity with mitotic activity, particularly if associated with increased vascularity and areas of necrosis, are suggestive of carcinomatous change and justify more extensive sampling of the material. A greater diagnostic difficulty is that of areas of atypia within the substance of the tumour (‘intracapsular carcinoma’). Though such changes may presage the development of frank carcinoma at some later stage if neglected, they do not seem to justify any further interference if parotidectomy has been carried out, since they (by definition) do not extend outside the tumour margins. Follow up, however, must be rigorous.
Histogenesis

It is generally accepted that pleomorphic adenomas are of intercalated duct origin, as noted by Batsakis et al (1992), with myoepithelial cell differentiation into epithelial and connective-tissue structures.

Electron microscopy has confirmed the presence of granules and other typical organelles in the duct cells and of myofilaments in the myoepithelial cells. The mesenchymal stromal components are probably due to their pluripotential properties as suggested by their immunochemical staining. Though they can appear dark and angular, spindle-shaped or resemble plasma cells, immunocytochemistry shows their typical double staining with epithelial (keratin) markers and mesenchymal markers, particularly S-100 protein, vimentin and myosin. However, as discussed in Chapter 1, the validity of the reported S-100 staining of myoepithelial cells has recently been called into question.

Positive immunocytochemical staining for antigens such as keratins, EMA, carcinoembryonic antigen, tissue plasminogen activator, lactoferrin, lectin receptors, immunoglobulins IgA and IgG and secretory piece component have also confirmed the epithelial and glandular nature of the other component of the tumour population.

Myoepithelioma

Despite the prominence of myoepithelial cells as a component of pleomorphic adenomas, tumours, solely of myoepithelial cells are rare. Unlike other adenomas, myoepitheliomas (strictly speaking) should show no structures overtly resembling glandular components. However, the term ‘myoepithelioma’ is probably more frequently used for tumours where myoepithelial cells form the bulk of the neoplasm but there are small areas of typical pleomorphic adenoma adjacent to them. Nevertheless, the latter may sometimes only be found if the specimen is examined widely. In terms of histogenesis, therefore, myoepitheliomas are variants of pleomorphic adenomas characterized by overwhelming myoepithelial proliferation. A carcinomatous variant is also recognized (Chapter 7), and from the viewpoint of histogenesis also, should be regarded as a variant of carcinoma in pleomorphic adenoma. However, in practical terms, these tumours have so distinctive an appearance, that many regard them as separate entities and the main consideration is not to confuse them with mesenchymal tumours.

From 50 cases or reports of this uncommon tumour, which has no distinctive clinical characteristics, Ellis and Gnepp (1988) have found the age incidence to average 40 years, but both children and the elderly can be affected. There is no apparent predominance in either sex; 48% of these tumours were in the parotid glands, 42% in the minor glands and the remaining 10% in the submandibular gland.

Microscopy

The two main types of myoepitheliomas are the spindle cell and the plasmacytoid. A mixed pattern of spindle and plasmacytoid cells is rare.
Spindle cell myoepitheliomas, the most common type, are highly cellular with little intercellular substance or stroma (Fig. 6.30). The spindle cells are elongated with faintly eosinophilic cytoplasm and pale central nuclei. They form variable patterns of interlacing streams of cells. The appearance thus resembles that of several types of mesenchymal tumour such as neurofibroma or fibrous histiocytoma and somewhat like these tumours may show variable degrees of aggressiveness. All grades between myoepithelioma to myoepithelial carcinoma may therefore be seen and mitotic activity and cellular pleomorphism are highly suspicious. However, aggressive behaviour may not be entirely predictable from the microscopic appearances.

Plasmacytoid myoepitheliomas are less cellular than the spindle cell type. The cells are rounded with hyaline, basophilic cytoplasm and an eccentrically placed nucleus, whilst the stroma is abundant, loose and myxoid (Figs 6.31 and 6.32). This variant is said not to have any potential for aggressive behaviour.

In contrast to the conventional view of plasmacytoid myoepitheliomas, Franquemont and Mills (1993) considered, on the basis of immunohistochemical findings, that they were a distinct type of plasmacytoid monomorphic adenoma. In two examples of the latter, unlike the three spindle cell myoepitheliomas, myogenous staining was negative but both were S-100 positive.

**Differential diagnosis**

Difficulty is only likely to arise in the case of spindle cell myoepitheliomas, particularly one arising in a minor gland when no glandular components or parent salivary tissue is present. In extreme cases, it might be necessary to resort to immunohistochemistry to detect the typical double staining of myoepithelial cells with epithelial (keratin) markers and mesenchymal particularly S-100 protein, vimentin and myosin.

Rarely, solitary plasmacytomas of salivary glands (Chapter 8) have been reported, but it is improbable that plasmacytoid myoepithelial cells would be confused with neoplastic plasma cells. However, in the unlikely event that there was any doubt the latter could be readily identified by staining for immunoglobulin or light chains.

**Monomorphic Adenoma**

**Warthin's Tumour (Adenolymphoma, Papillary Cystadenoma Lymphomatosum)**

The alternative term, 'adenolymphoma', for Warthin's tumour has the obvious objection that the lymphoid component is certainly not lymphomatous and lymphomatous change is exceedingly rare. The term, 'papillary cystadenoma lymphomatosum', describes the main features, but is clumsy.

**Incidence**

Warthin's tumour consists of a characteristic eosinophilic glandular epithelial component and a stroma of lymphocytes which may form follicles.
Warthin's tumour is the most common monomorphic adenoma. It accounts for 14.4% of all salivary gland tumours and hence is, overall, the second most common tumour to pleomorphic adenoma. The frequency may be even higher as suggested by the finding of multiple asymptomatic nodules in computerized tomography of the parotid glands. Indeed the finding of bilateral or multiple tumours, the occasional cases of familial tumours and the fact that it is found only in the parotid raises doubts as to whether Warthin's tumour is a true neoplasm.

Clinical features

Of the 335 Warthin's tumours in the BSGTP material, all but two were in the parotid glands. Even the two cases said to have been in the submandibular glands, showed no submandibular salivary tissue and it seems likely that the posterior pole of this gland had been mistaken clinically for the nearby lower pole of the parotid. Nevertheless, Van der Wal et al (1993) were able to find 10 examples of extraparotid Warthin's tumours. Most were intraoral but three were in the larynx.

Warthin's tumour has been reported in various intraoral sites, but in these minor glands it is necessary to distinguish ductal hyperplasia with oncocytic change and reactive lymphoid proliferation, from a true Warthin's tumour. It has also been suggested that sialadenoma papilliferum, a rare tumour found mainly in intra-oral glands, is a variant of Warthin's tumour, but this seems unlikely.

The mean age for Warthin's tumours in males is 62.6 ± 10.9 years, with an age range of 25-92 years; the mean age for females is similar (62.7 ± 12.5 years with a range of 12 to 87 years). However, the peak incidence is in the seventh decade for men and in the sixth decade for women.

A mysterious aspect of these tumours is the apparent change in the sex incidence, as reviewed by Eveson and Cawson (1986). This change has ranged from a male predominance of 10 to 1 (Foote and Frazell, 1953) or 7 to 1 in 306 cases reviewed by Chaudhry and Gorlin (1959), to 1.5 to 1 in the 278 cases accessioned by the BSGTP and the series reported by Yoshimora and Gabka (1979). Kennedy (1983) reported an equal sex incidence in a small series while Dietert (1975) has traced the declining male predominance in the period between 1950 and 1973. Lamelas et al (1987) have also confirmed the rising female incidence of this tumour and there seems therefore genuinely to have been a relative decline in the incidence of Warthin's tumours in males. However any explanation can only be speculative.

Warthin's tumours appear to be uncommon in Blacks and this may explain its lower incidence in American series apart from that of Lamelas et al (1987) who also found them to constitute 14.4% of their 917 parotid tumours.

Warthin's tumours typically grow slowly to form soft, painless swellings usually at the lower pole of the parotid. The average duration of symptoms is a little under two years but among our material, the shortest duration of symptoms was three weeks and 41% of the patients had been aware of the swelling for six months or less. The longest duration of symptoms was said to have been between 10 and 20 years.
Pain may be reported by a minority (7% of cases, in our material but more frequently in other series) and is more frequent in the infarcted type of tumour described later. Rarely, pain can be severe and be felt as earache. Other complaints have been variations in the size of the swelling, occasionally associated with eating, and fairly frequently, a sudden expansion of the swelling had caused patients to seek help. In one patient, where the tumour involved the eustachian cushion, there was deafness and tinnitus. In another, there was facial weakness, but there were no cases of facial palsy. One of our patients, a cold store worker, noticed his parotid swelling when it became firm in his working environment.

Overall therefore, Warthin's tumours appear capable of giving rise to a greater variety of symptoms than other benign tumours, and the complaints of pain and of sudden increase in size of the mass (presumably as a result of cystic expansion) may suggest malignancy.

Warthin's tumours are also more frequently associated with a second tumour than any other and the most frequent combination appears to be a Warthin's tumour with a pleomorphic adenoma. The tumours can be synchronous, metachronous, in the same gland or on opposite sides.

Lefor and Ord (1993) reported a case of multiple, synchronous bilateral Warthin's tumours associated with pleomorphic adenoma. They found only three reports of multiple, synchronous bilateral Warthin's tumours and reviewed the frequency and types of other associated tumours.

**Macroscopic and microscopic features**

Most tumours are well circumscribed and > 50% of them are ≤ 3 cm across. Tumours > 10 cm are rare. In 10% of cases tumours may be multifocal (Fig. 6.33).

Despite gross circumscription there is only a thin capsule which is incomplete in most cases or even absent in a minority and these tumours readily rupture during removal.

The microscopic appearances are usually highly characteristic and unmistakable. The epithelium is double-layered, but most striking are the tall columnar, eosinophilic and granular epithelial cells, usually thrown into multiple folds and lining cystic cavities into which they form papillary projections (Fig. 6.34). The nuclei tend to be uniform in size and evenly arranged near the middle of the cell or nearer the free surface. The underlying cells are smaller, irregularly disposed; they are also fewer in number and sometimes not discernible (Fig. 6.35). Alternatively, these cells may sometimes form a basal layer and resemble myoepithelial cells. Sometimes, the luminal cells are intensely oncocytic (dark cells) with pyknotic nuclei (Fig. 6.36). Occasionally such cells are extruded into the cyst cavity. As with other oncocytic tumours, the dark cells can be shown by electron microscopy to have a higher mitochondrial content than the predominant epithelial cells.

Among the oncocytic cells, mucous metaplasia is common, with the result that there are goblet cells (Fig. 6.37), which stain strongly with PAS, and secretion of mucus into the cyst cavities.
By electron microscopy, the columnar epithelial cells are densely packed with swollen mitochondria which often contain so many cristae as to appear stacked together (Fig. 6.38). Many also contain dense bodies which are enclosed by a single unit membrane and have regularly lamellated contents.

The cystic spaces are variable in size, frequently being no more than lacunae between the folds of epithelium but occasionally forming the major part of the mass with only mural tumour tissue.

In these spaces, there is frequently eosinophilic material. Cholesterol clefts, epithelial and inflammatory cells are sometimes present while less often there are laminated structures resembling corpora amylacea (Fig. 6.39).

The lymphoid component consists of small lymphocytes with a few plasma cells, histiocytes and mast cells. Germinal follicles are present in the majority. A peripheral sinus may be discernible.

**Variants**

Mucous or sometimes, squamous metaplasia of the epithelium is common. Such changes are rarely widespread but may occasionally be sufficient to mimic a mucoepidermoid carcinoma (Figs 6.40 and 6.41). Ciliated epithelium, as noted by Warthin (1929), may be found. It is not an artefact as has been sometimes claimed, but is rarely seen (Figs 6.42 and 6.43).

An exceedingly rare variant is extensive sebaceous differentiation. This has been said to be the result of metaplasia, but sebaceous lymphadenoma (it is unclear why the sebaceous tumour was given the latter term rather than 'sebaceous adenolymphoma') is widely regarded as a distinct entity.

The ratio of epithelium to lymphoid stroma can vary widely. In the histological subclassification by Seifert et al (1980), 'typical' Warthin's tumours had a lymphoid component accounting for 50% of the tumour, in 'stroma-poor' tumours it formed < 30% while in 'stroma-rich' it formed ≥ 70%. In a fourth type, termed 'metaplastic', squamous metaplasia was extensive. This last type formed 7.5% of their cases, but up to 50% of them had been irradiated.

However, we find that stroma forms between 30 and 70% of typical tumours and that > 80% of these tumours conform to this criterion. Stroma-rich (Fig. 6.44) and stroma-poor (Fig. 6.45) by contrast only accounted for 5% each (Eveson and Cawson, 1986). As in the cases of Seifert et al (1980), patients with stroma-poor tumours were significantly older. No so-called 'metaplastic tumours' were found among our 335 specimens and only localized foci of squamous metaplasia were seen in a minority of infarcted Warthin's tumours.

**Stroma-poor Warthin's tumours**

Rarely, lymphoid stroma may be apparently completely absent and the tumour appears as a papillary cystadenoma. However, the tall, columnar, oncocytic epithelial cells remain
distinctive. We suggest that this is the only type of papillary cystadenoma which can be confidently categorized as benign.

**Fibrotic, infarcted and metaplastic Warthin's tumours**

Mild stromal fibrosis may be seen in nearly 50% of cases, but in a few there can be almost complete fibrous replacement of the lymphoid tissue (Fig. 6.46). Less well recognized are infarcted Warthin's tumours which formed 6% of 323 Warthin's tumours in our material (Everson and Cawson, 1989) in which there may be epithelioid granuloma formation (with or without giant cells); this may be so extensive as to cause confusion with other granulomatous diseases such as tuberculosis (Fig. 6.47). Squamous metaplasia of the cyst linings was present in 35% of these cases (Fig. 6.48), but was usually focal and mild.

Granulomatous reactions in Warthin's tumours appear to have been first mentioned by Foote and Frazell (1954) who considered them to be foreign-body reactions to leakage of secretion. By contrast, Patey and Thackray (1970) who described widespread necrosis in two of these tumours, considered that it was probably the result of infection for which the cyst contents would form an ideal culture medium for blood-borne bacteria. However, we could find no evidence of bacterial infection in our material and considered that the changes were more suggestive of infarction. In support of such an idea is the fact that, as noted by Warthin (1929), these tumours are poorly vascular with a limited arterial supply and few blood vessels within them. The fact that Warthin's tumours only exceedingly rarely grow > 60 mm in diameter possibly suggests that further growth is limited by their blood supply.

Seifert et al (1980) have described yet another variant, which they term 'metaplastic'. This is characterized by florid squamous metaplasia of the epithelium, formation of pseudocysts and hyalinization of the lymphoid stroma. Though there are some features in common with the so-called 'infarcted' type, there are notable differences, in particular that 40% of the metaplastic but none of the infarcted variants had a history of irradiation. Curiously also, there was a strong predominance of males (4:1) with infarcted Warthin's tumours, but metaplastic tumours were more common in females.

**Malignant change, concomitant and secondary tumours**

Carcinomatous change in Warthin's tumours (Chapter 7) has only exceedingly rarely been reported and may in some cases, have been secondary to irradiation.

The undifferentiated carcinoma with lymphoid stroma (malignant lymphoepithelial lesion), seen mainly in Eskimos and Southern Chinese, is a different entity, as discussed later.

Lymphomatous change in Warthin's tumour is particularly rare but a few cases have been recorded over the decades as discussed later (Chapter 8) with other lymphomas of salivary glands.

Yet another possibility and a potential diagnostic hazard, is the association of Warthin's tumour with other salivary gland tumours such as pleomorphic adenoma and mucoepidermoid or other carcinomas. In our material, 4 of 278 Warthin's tumours were associated; two were pleomorphic adenomas and two were oncocytomas. In the material
described by Seifert et al (1986), 3% of Warthin's tumours were associated with others such as basal cell carcinoma and extraoral tumours such as laryngeal cancer and malignant lymphoma.

Secondary deposits of distant tumours have also been reported in the lymphoid component of Warthin's tumours. However, it is important not to mistake a Warthin's tumour developing in a cervical lymph node near the parotid gland for a metastasis.

**Differential diagnosis**

The diagnosis of Warthin's tumour is unlikely to be made clinically, unless it is suggested by rapid changes in size or consistency. If the mass appears to be cystic and aspiration is carried out, a yield of brownish fluid strongly suggests a Warthin's tumour. Usually, however, these tumours are treated like pleomorphic adenomas and the diagnosis is made postoperatively.

The only source of possible confusion microscopically is likely to be extensive granuloma formation and necrosis. Either tuberculosis or sarcoidosis may therefore need to be excluded, but only rarely.

**Treatment and prognosis**

Excision (superficial or total conservative parotidectomy) is curative. Small foci of incipient tumour formation may also be found in the surrounding parotid tissue. Such multiple foci almost certainly account for the rare recurrences that have been reported. However, the infrequency of such reports suggest that small Warthin's tumours may spontaneously abort.

**Histogenesis**

The widely accepted view of the histogenesis of Warthin's tumours is also related to their site of origin. This theory, originally proposed by Albrecht and Arzt (1910) proposes that there is neoplastic proliferation of ectopic salivary gland ducts within intra- or paraparotid lymph nodes. Ectopic ducts, or even acini, are in fact a frequent finding in this lymphoid tissue in children. Moreover, Azzopardi and Hou (1964) have confirmed the presence of minute Warthin's tumours forming from ductal elements in parotid lymphoid tissue (Fig. 6.49).

The absence of lymphoid tissue from other salivary glands explains the development of these tumours only in the parotid glands, but it is unclear whether the lymphoid component of the tumour is that of a normal lymph node, a lymphocytic reaction or a combination of both. One study using B- and T-cell markers, confirmed the predominance of T-lymphocytes and that the lymphoid tissue was compatible with being normal lymphoid tissue, but another showed a predominance of B-cells similar to that seen in reactive nodes. A more recent study (Caselitz et al, 1984) confirms a distribution of T- and B-lymphocytes like that of normal lymphoid tissue.
Further to complicate this issue is the finding by Thackray and Lucas (1974) of areas of oncocytic change and adenomatous proliferation associated with varying degrees of lymphoid proliferation, including follicle formation, but clearly not developing in lymph nodes. A similar example is shown of a cystadenoma identical to a Warthin's tumour, apart from the absence of any lymphoid tissue (Fig. 6.50). This may be described as a 'stroma-free Warthin's tumour'. The distribution of germinal follicles, particularly those at the tips of the papillary projections of Warthin's tumours, also suggests secondary accumulation of lymphoid tissue.

The epithelium is positive for such markers as IgA, secretory components, lactoferrin and carcinoembryonic antigen and therefore seems to be of duct origin.

It may be noted incidentally that there is little to support the idea (Allegra, 1971) that Warthin's tumours are immunologically mediated lesions comparable to Hashimoto's disease or Sjögren's syndrome. That this is not the case is shown by the circumscribed nature of these tumours, the lack of parenchymal destruction and the composition of the lymphoid component. Moreover, there is no autoantibody production, no systemic manifestations and no association with any of the recognized autoimmune diseases.

In brief, therefore, it seems likely that Warthin's tumours generally develop from ectopic salivary ducts within parotid lymphoid tissue which proliferates and may undergo reactive changes, possibly as a response to the neoplastic epithelial component.

**Oncocytoma (Oxyphilic Adenoma)**

Oncocytomas are rare tumours. In the series by Seifert et al. (1986) they formed < 0.5% of epithelial salivary gland tumours and in our material, ≤ 0.8%. They are predominantly tumours of those over middle age, and women, usually in the seventh or eight decade are more likely to be affected. The parotid glands are by far the most frequent site; these tumours are slow-growing and may rarely be bilateral.

True oncocytomas must be distinguished from multifocal nodular hyperplasia and other oncocytic lesions, as described by Palmer et al. (1990) and discussed below. Hartwick and Batsakis (1990) have also summarized the salient features of oncocytic lesions other than Warthin's tumours and the cellular characteristics of salivary gland oncocytes.

**Microscopy features**

The appearance of oncocytomas is distinctive. The tumour cells are uniform in size, plump and rounded or polygonal with a granular eosinophilic, swollen cytoplasm and a central nucleus. They form trabeculae, empty duct-like structures or less frequently, microcysts, and are surrounded by fine fibrous septa. A few of the cells ('dark cells') may be compressed, and more darkly staining, whilst others may be clear (Fig. 6.51). A few lymphocytes may infiltrate the stroma and there is then the risk of mistaking an oncocytoma for a stroma-poor Warthin's tumour if the columnar form of the latter's epithelial cells is not obvious.
Occasional clear cells and their transition from oncocytes may sometimes be seen (Figs 6.52 and 6.53). However, oncocytomas consisting only of clear cells are exceedingly rare and are discussed later with other clear-cell tumours (Chapter 7). In our material clear-cell oncocytomas were found only in those tumours which were associated with multinodular oncocytic hyperplasia and large aggregates of clear cells were sometimes also a feature of multinodular oncocytic hyperplasia itself.

Calcifications (psammoma bodies) are a rare finding and in our experience were found only in pleomorphic adenomas with oncocytic change but not in true oncocytomas (Palmer et al, 1990).

By electron microscopy the oncocytes are filled with mitochondria of variable size, with many cristae and contain lamellated structures. In paraffin sections, these mitochondrial-rich cells stain with PTAH and this may be used if necessary, to confirm the nature of oncocytes.

**Multifocal nodular oncocytic hyperplasia**

This change was described by Schwartz and Feldman (1969) and termed by them, 'multifocal oncocytic adenomatous hyperplasia'. These foci have a solid trabecular structure, are small (≤ 1 cm in size), multiple and interspersed by remnants of normal salivary gland (Fig. 6.54). They may also be seen adjacent to a typical oncocytoma, so that it seems possible that the latter can arise by confluence of these foci as proposed by Johns et al (1977). Clear-cell change is more frequently seen in multifocal nodular oncocytic hyperplasia than in oncocytoma and can then be easily confused with a clear-cell tumour infiltrating the gland (Fig. 6.55).

**Differential diagnosis**

Foci of oncocytic change, occasionally extensive, can be seen in other tumours such as pleomorphic adenomas or even in adenocarcinomas. Oncocytosis (Chapter 3) can also be seen as an age change in normal duct and other epithelia. Since oncocytomas are completely benign, it is important to differentiate them from oncocytic change in pleomorphic adenomas which, though also benign, are far more difficult to manage. In an analysis of 26 tumours, previously categorized as oncocytomas, Palmer et al (1990) found that nine of them were pleomorphic adenomas with oncocytic change. Even more important is to recognize a malignant tumour with oncocytic change. Further sampling of some specimens may therefore be necessary.

The differentiation of oncocytomas from multifocal nodular oncocytic hyperplasia is probably little more than a matter of terminology in that both are benign conditions, though foci of multifocal nodular hyperplasia may be the source of recurrences if the entire gland has not been removed.

By contrast, the recognition of clear-cell oncocytomas is important as they must be differentiated from other clear-cell tumours, all of which, other than oncocytomas, are malignant, as discussed later.
Histogenesis

The similarities of the cells of oncocytomas to those of Warthin's tumours, both by light and electron microscopy, suggest that they are of striated duct origin and this appears to be confirmed by enzyme histochemistry. Ultrastructurally, oncocytoma cells and the oncocytic cells of Warthin's tumours are packed with mitochondria.

The age of the patients and the appearance of identical-appearing cells in the process of oncocytosis in other elderly patients indicates that ageing plays a part in the development of these tumours.

Treatment and prognosis

Oncocytomas are benign and excision is curative. There have been occasional reports of recurrences, probably due to other nodules of tumour tissue in the gland or possibly to the development of a second primary tumour.

Reports of metastasizing oncocytomas are difficult to authenticate but Goode and Corio (1988), among others, believe that apparently benign oncocytomas can occasionally metastasize and also note that some oncocytic adenocarcinomas had previously been reported as oncocytomas, as discussed in the following chapter. Seifert et al (1986) also describe oncocytomas as 'usually benign' and thus imply that malignant variants may not be initially recognizable.

Most authorities, however, regard oncocytic adenocarcinomas as distinct entities which should be recognizable as such. Moreover, oncocytoma is an uncommon tumour and any cytologically benign but malignant variants are unlikely to be a significant hazard, particularly in those centres where all parotid salivary gland tumours are treated by parotidectomy.

Diffuse Oncocytosis

Oncocytosis is non-neoplastic and even more uncommon than an oncocytoma but may occasionally involve virtually an entire parotid gland. Diffuse hyperplastic oncocytosis gives rise to a soft swelling and, like localized oncocytic change, particularly affects the elderly.

Microscopically, oncocytosis is distinguishable from an oncocytoma particularly by its extent, lack of circumscription, persistence (in many cases) of ducts and by the progressive transition at the periphery of normal parotid cells to oncocytes (Fig. 6.56).

Basal Cell Adenomas

Basal cell adenomas form the main group of duct adenomas but a canalicular type can sometimes be distinguished from the others. Duct adenomas are the most common single type of monomorphic adenoma after Warthin's tumour, and account for about 20% of all adenomas. However, the terminology or classification of these tumours is still somewhat controversial and it is often by no means easy to fit some of these tumours into one or other of these categories with absolute certainty. This group (including both basal cell and canalicular-adenomas) formed 7% of parotid tumours, 11% of sublingual tumours, where they
were as frequent as pleomorphic adenomas, and 10% of minor gland tumours in our material. In the minor glands, the upper lip is the site of predilection. By contrast, duct adenomas are rare in the submandibular glands and form barely 2% of the tumours there. In other words, 75% of duct adenomas are in the parotid glands, 22% are in the minor glands and very few are in the remainder.

In their main site, the parotid gland, duct adenomas have a less well-defined age and sex distribution than pleomorphic adenomas and Warthin's tumours. In males, the peak incidence appears to be in the seventh decade. In females, they appear to be most frequent between the fifth and eighth decades. At some ages there appears to be a heavy female preponderance but these findings are probably distorted by the relatively small number of these tumours available for analysis.

Insofar as it is possible to generalize about this group of histologically diverse tumours, they form slow-growing, well-circumscribed swellings.

**Tubular, trabecular, solid and membranous adenomas**

Basal cell adenomas consist of small, darkly staining epithelial cells with little cytoplasm. These are in tubular or trabecular configurations or solid masses.

**Tubular type**

This consists of tubules containing eosinophilic secretions (Fig. 6.57). The tubules have an epithelial lining and a mantle layer of myoepithelial cells: the latter also appear as strands extending between the tubules. However, the myoepithelial cells may be less numerous and inconspicuous. The stroma is usually scanty and unremarkable.

**Trabecular type**

This is probably a variant of tubular adenomas. It consists of a monotonous pattern of cords, uniform in width, of darkly staining cells which are not readily distinguishable into duct and myoepithelial cells (Fig. 6.58). The stroma is sparse and featureless. A rare variant undergoes oncocytic change and may be mistaken for an oncocytoma (Fig. 6.59).

It is common to see combinations of both tubular and trabecular configurations in the same tumour (Fig. 6.60). A rare variant of tubular-trabecular adenomas shows myoepithelial stromal proliferation (Fig. 6.61). Cystic duct adenomas are sometimes distinguished from the other types, but may merely represent degenerative changes in a canalicular adenoma. They consist of closely apposed microcysts with walls of multilayered darkly staining epithelial cells. PAS-positive or, sometimes, crystalline material, may be found within the cysts. Degenerative changes may leave blood and degenerating epithelial and other cells in the tumour.

**Solid-type basal cell adenomas**

These consist of broad bands or solid masses of darkly staining cells with little cytoplasm (Fig. 6.62). The outermost layer may show a tendency to palisading while the inner
cells are more haphazardly arranged or may have a whorled arrangement. This epithelium is sharply demarcated from the stroma by a PAS-positive basal membrane while the stroma itself is loose, may be highly vascular and may contain elastic tissue.

Like tubular adenomas these tumours appear to be derived from intercalated duct cells.

In addition to the types described above, Dardick et al (1992) have reported a rare variant with a solid-cribriform pattern resembling an adenoid cystic carcinoma, but lacking duct lumens. In two such cases, one stained for muscle-specific actin as well as for high-molecular-weight cytokeratins.

Membranous basal cell adenoma

Very rarely, a thick, eosinophilic and PAS-positive hyaline layer surrounds the epithelium, which may contain lumens (Fig. 6.3). Hyaline material may also be present within the epithelial islands. Unlike other monomorphic adenomas, this variant is usually multilobular (probably as a consequence of a multicentric origin) and less well-encapsulated. It can also contain foci of normal salivary tissue to add to the impression of invasiveness and increase its similarities to an adenoid cystic carcinoma. The appearance is not significantly different from that of a dermal cylindroma.

These tumours most frequently affect the parotid gland and when in this site may be associated with multiple similar (turban) tumours of the scalp, trichoepithelioma and eccrine spiradenoma, and are sometimes therefore, also termed 'dermal analogue tumour of the parotid'. This multiple tumour diathesis may be a genetic disorder affecting a multipotential duct reserve stem cell. If so, membranous adenomas which are not associated with skin tumours may represent incomplete expression of this genetic syndrome.

This variant has been reviewed in detail by Ellis and Gnepp (1988) and by Hyma et al (1988) who report malignant change in a membranous adenoma in a 66-year-old woman with this tumour syndrome and also a carcinoma of the breast.

Canalicular Adenoma

Canalicular adenomas consist of duct-like structures or cords of columnar or cuboidal epithelial cells but lack a mantle of myoepithelial cells (Fig. 6.64). Cyst formation may be prominent, while degeneration of the stroma may leave it virtually structureless and containing little more than the mere outlines of blood vessels.

Nelson and Jacoway (1973) drew attention to the predilection of canalicular adenomas for the upper lip (Figs 6.65 and 6.66) where examples which had a cribriform-like pattern have been mistaken for adenoid cystic carcinomas.

Differential diagnosis

The chief risk is that of mistaking some of these tumours for adenoid cystic carcinomas as noted by Nelson and Jacoway (1973). As already mentioned, canalicular adenomas can form cribriform areas while basal cell adenomas (particularly the membranous
variant with its hyaline material) can also resemble areas that may be seen within an adenoid cystic carcinoma. The presence of stromal degeneration is a feature which helps to distinguish canalicular from tubular or trabecular adenomas and from adenoid cystic carcinomas. The absence of myoepithelial cells surrounding the duct-like structures also helps to distinguish canalicular adenomas from tubular-trabecular basal cell adenomas.

Nevertheless, an extensive search in many fields may sometimes be necessary to confirm clear encapsulation and lack of signs of invasive activity before the diagnosis of adenoid cystic carcinoma can be dismissed. If the biopsy is too small it may even be impossible to make the necessary distinction.

Williams et al (1993) using a wide range of immunostains, concluded that basal cell adenomas (11 cases) could not be distinguished from basal cell adenocarcinomas (23 cases) by this means.

**Multifocal Monomorphic Adenomatosis**

Very occasionally, a lesion resembling a multiplicity of duct adenomas appears in minor salivary glands. In an affected gland there may be literally dozens of these foci, some of which are discrete and circumscribed and are then difficult to distinguish from a tubulo-trabecular basal cell adenomas (see Figs 6.80 and 6.81, p 115). These individual foci are typically ≤ 5 mm in diameter. However, in other areas they merge imperceptibly into normal gland parenchyma and are not therefore thought to be neoplastic.

**Sebaceous Adenoma and Sebaceous Lymphadenoma**

Both of these tumours are rare, but can be assumed to have arisen from sebaceous tissue found in normal parotid glands and are not therefore skin tumours. Sebaceous elements can sometimes also be seen in pleomorphic adenomas.

The sebaceous lymphadenoma resembles Warthin's tumour but with sebaceous cells and sebaceous cysts in place of the oncocytic cells (Fig. 6.67). Unlike typical Warthin's tumours, the sebaceous cells form solid masses and there is no infolding of the epithelium in the cysts, which therefore have smooth walls. The sebaceous cells are identifiable by Sudan red-positive fat in the cytoplasm and fat spaces may be seen in the lymphoid stroma. Occasionally there is some squamous metaplasia.

An intermediate form, with sebaceous elements in an otherwise conventional Warthin's tumour may also be seen. The 'pure' sebaceous adenoma is even more uncommon and consists of solid masses of sebaceous tissue in a fibrous stroma (Fig. 6.68).

**Duct Papillomas**

Three types of duct papilloma are recognized, namely, inverted duct and intraduct papillomas and sialadenoma papilliferum. All are rare.
Inverted duct papilloma

Inverted duct papilloma of a salivary gland is an exceedingly rare tumour which differs microscopically from the inverted papillomas of the nasal cavity and from the even more rare oral mucosal inverted papillomas which appear to arise from surface epithelium (Fig. 6.9).

Clinically, patients have been adults between the ages of 33 and 66 years. In these patients, the tumour typically gave rise to smooth, discrete swellings 1-1.5 cm in diameter, in various sites within the oral cavity.

Microscopy

Inverted duct papillomas usually form just within the orifice of a duct and their epithelium may adjoin that of the surface mucosa. The tumour consists of thick or bulbous papillae covered by basal or squamous cells. The papillary overgrowth fills the neighbouring duct lumen and also extends into the duct wall, but does not infiltrate the lamina propria (Fig. 6.70). A few goblet or columnar cells may be found in the covering epithelium and microcysts lined by squamous or columnar epithelium occasionally form.

Excision appears to be curative and there is no evidence of the propensity for recurrence that is shown by inverted papillomas of the nasal cavity.

Intraduct papilloma

Intraduct papilloma is even more uncommon than other duct papillomas. It differs from the inverted duct papilloma in its origin which is deeper in the salivary gland duct.

Microscopy

The intraduct papilloma consists of fibrovascular papillae covered by columnar or cuboidal epithelium forming a mass which distends the duct lumen to form a cyst-like cavity (Fig. 6.71). Unlike the inverted duct papilloma, the intraduct papilloma does not extend into the duct wall but may obstruct the duct to cause secondary ductal dilatation proximally.

Excision is curative.

Sialadenoma papilliferum

This rare, exophytic salivary gland tumour was given its name by Abrams and Finck (1969) because of its close resemblance to the sweat gland tumour, ‘syringocystadenoma papilliferum’. The largest series to date (29 cases) has been reviewed in detail by Ellis and Gnepp (1988).

Any age from infancy to old age can be affected but the mean age of incidence is 59 years. Men have accounted for twice as many of the reported cases as women. The palate, particularly the region of the junction of hard and soft palate, is by far the most frequently affected site. Most other cases have been in the minor glands but a single example in the
parotid gland was reported by Abrams and Finck (1969).

The characteristic clinical feature of this tumour is that it forms a painless exophytic growth that resembles a papilloma, but is related to a salivary gland.

Microscopy

The surface closely resembles a squamous-cell papilloma in that it is covered by stratified squamous epithelium thrown up into papillae, each with a fibrovascular core (Fig. 6.72). However, this epithelium merges, more deeply, with ductal epithelium which proliferates to form dilated duct-like structures and often, more deeply still, microcysts with papillary projections into their cavities (Fig. 6.73). Proliferation of small ducts may be seen in the base of the lesion. The cytoplasm of all these ductal cells is typically eosinophilic. This glandular epithelium is covered by a double layer of cells, the outermost of which are tall, columnar and eosinophilic.

Local excision appears to be curative.

So-called 'Clear-cell Adenoma'

The tumours are no longer included in the current WHO classification. Though limited areas of some tumours may have an appearance which could be interpreted in this way, the existence of clear-cell adenoma as an entity has not largely been dismissed.

Most clear-cell tumours are malignant, despite a cytologically benign appearance and in our view the only truly benign clear-cell tumour is the clear-cell variant of oncocytoma discussed earlier. Many tumours formerly categorized as clear-cell adenomas would now be designated epithelial-myoepithelial carcinomas. Clear-cell tumours, as a group, are therefore discussed later (Chapter 7).

So-called 'Papillary Cystadenoma' and 'Mucinous Cystadenoma'

We consider the term 'papillary cystadenoma' is a possible cause of confusion. Probably the only benign papillary cystic tumour is in cytological terms a Warthin's tumour which lacks a lymphoid stroma (Figs 6.74 and 6.75). Great caution is needed in microscopical interpretation of a papillary cystic tumour, especially if there is any mucin production. Like those in the thyroid gland, most papillary cystic salivary gland tumours are carcinomas, despite their cytologically benign appearance. One such tumour, in our experience, was categorized originally as an adenoma, widely excised but caused the death of the patient from widespread metastases after an asymptomatic period of 15 years. As discussed later, papillary cystic adenocarcinomas frequently have a deceptively benign cytological appearance and it is these tumours which are likely to have been categorized as papillary cystic adenomas in the past.

We have equal reservations about the rare tumour termed 'mucinous cystadenoma'. Little information is available as to its response to treatment and its benign cytological appearances may be as deceptive as those of papillary cystic adenocarcinomas. Even if true mucinous cystadenomas are an entity, there may be considerable difficulty in differentiating
them from their more common malignant counterparts.

**Treatment and Prognosis of Monomorphic Adenomas**

As already discussed, most of these adenomas are well circumscribed and recurrence should not be expected after complete excision. At the same time, the behaviour of these tumours is not always as predictable as might be hoped. Since it is not possible to distinguish monomorphic from pleomorphic adenomas clinically, conservative parotidectomy is likely to be carried out.

A possible limitation of fine-needle aspiration biopsy for monomorphic adenomas is that some of them, though undoubtedly benign, can be multiple. Others, such as some basal cell adenomas can be difficult to differentiate from basal cell adenocarcinomas or adenoid cystic carcinomas even in a section. Basal cell adenocarcinomas, in particular, may not show obvious cytologic features of malignancy. Yet other problems are that of the imperfect categorization of some (particularly clear-cell tumours) as completely benign or low-grade malignant.

These difficulties should not be exaggerated in that these are, overall, rare tumours. However, they form another strong argument for parotidectomy (or its equivalent in other glands) for all adenomas, rather than to attempt enucleation. In those which prove ultimately to be of low-grade malignancy, spread may sometimes not become apparent for a decade and the risk of recurrence is likely to be greatly reduced, if parotidectomy is carried out.

**Tumour-Like Lesions**

Both of the WHO classifications include sialadenosis as a tumour-like lesion. However, adenomatoid hyperplasia of minor salivary glands which is more readily mistaken for a tumour, and multifocal monomorphic adenomatosis are not included in these classifications.

**Sialadenosis**

Sialadenosis (sialosis) is an uncommon type of non-inflammatory swelling, particularly of the parotid glands, typically associated with a variety of systemic diseases (Table 6.3) but sometimes affecting otherwise normal persons, and is of uncertain pathogenesis.

**Table 6.3** Some conditions associated with sialadenosis

<table>
<thead>
<tr>
<th>Alcoholism</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other endocrine diseases</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Drugs: particularly sympathomimetics</td>
<td>Bulimia</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>
Clinically, most patients are between the ages of 40 and 70 years. The swellings are soft and typically affect the parotid glands symmetrically (Fig. 6.76). The complaint may sometimes be that swellings have become so large as to give the patient a hamster-like appearance. Diseases that may be associated include diabetes mellitus or rarely, almost any other endocrine disorder, or alcoholism. Sialadenosis, said by Fulop (1989) to be common in myxoedema, was recognized over 60 years ago but references to it are scanty. Sialadenosis can also be drug-induced by agents such as sympathomimetic drugs in long-term use for asthma, and some of the older anti-hypertensive drugs, particularly guanethidine. Nevertheless, in a significant number of patients, no underlying disorder can be found.

Sialadenosis has also been said to be a complication of gross malnutrition but since the latter has also been said to be responsible for glandular atrophy and fatty replacement, it seems uncertain which is the main cause of salivary gland swelling associated with famine conditions. However, salivary gland enlargement, in which aspiration cytology showed acinar hypertrophy but paucity of ducts (a state compatible with sialadenosis though not described as such), has been reported by Hasler (1982) in anorexia nervosa and it is also seen in some cases of bulimia.

**Aetiology**

The microscopic changes resemble those produced by experimental denervation of salivary glands. It has therefore been suggested that the diseases and drugs which can be associated with this condition may induce a neuropathy which interferes with salivary secretion. Seifert et al (1986) argue strongly for autonomic neuropathy or interference with autonomic function as the underlying mechanism. This may be the case in diabetes mellitus where autonomic neuropathy is a recognized complication, and in drug-induced sialadenosis. However, it seems paradoxical that sympathetic agonists such as salbutamol as well as guanethidine, whose main effect is to inhibit release of noradrenaline from sympathetic terminals, should have a similar effect on salivary tissue.

**Microscopy**

The main features are enlargement of acinar cells to double or treble their normal size. These cells are typically packed with large secretory granules but may appear vacuolated when the secretory granules are of low optical density (Figs 6.77 and 6.78).

As a result of the swelling of the acini, the duct system may become slightly compressed but there is no inflammatory infiltrate.

Diagnosis depends largely on the clinical features and medical history but obsolete confirmation depends on aspiration cytology or biopsy.

Treatment is unsatisfactory. Endocrine-associated sialadenosis is usually persistent even when control of the underlying disease is achieved. Drug-associated sialadenosis may regress when the responsible drug is withdrawn.
Salivary gland changes in alcohol abuse

Although sialadenosis may occasionally be seen in those who abuse alcohol, an autopsy study of parotid and submandibular glands in alcoholics by Scott et al (1988) found significant changes only in association with cirrhosis. In cirrhotic patients, the parotid glands contained increased adipose but decreased acinar tissue, while the submandibular glands showed only increased fat content compared with controls. Neither grossly detectable parotid swelling nor acinar hypertrophy characteristic of sialadenosis was found. However, it was suggested that mild parotid enlargement might have been detectable clinically but was not evident after death.

Adenomatoid hyperplasia of minor mucous salivary glands

Rarely, hyperplasia of mucous acinar cells can give rise to a tumour-like swelling. The mucous glands of the palate are most frequently affected. The aetiology is unknown.

Clinically, the hyperplastic mass forms a smooth painless swelling usually to one side of the midline of the hard or soft palate but occasionally other intraoral sites such as the retromolar region may be affected (Fig. 6.79).

Microscopy

There is hypertrophy of the gland lobules, but the individual mucous acini appear normal. Sometimes there are focal areas of mucous extravasation.

These lesions need to be excised to confirm the diagnosis and to exclude the possibility of a tumour, and when this is done, they do not recur.

Multifocal monomorphic adenomatosis

In this uncommon condition of unknown aetiology, multiple small foci of what appear to be baal cell adenomas (Figs 6.80 and 6.81) form in an otherwise normal gland. The significance of this anomaly is unknown but it is important not to mistake it for spread of a well-differentiated basal cell adenocarcinoma.

Note

1. A. S. Warthin (1866-1931), American pathologist.
The Pathology and Surgery of the Salivary Glands
R. A. Cawson, M. J. Gleeson, J. W. Eveson

Chapter 7: Carcinoma of salivary glands

Introduction

In terms of registration in England and Wales, cancers of salivary glands (ICD 142) form a little under 0.3% of all cancers. They were also estimated to form 0.3% of all malignant tumours in Sweden.

Internationally, there appear to be wider variations, some of which may depend on criteria for defining malignancy. In Norway, for example, the incidence appears to be half that of other European countries. Nevertheless, this lower recorded morbidity is associated with a considerably higher relative mortality. There are also other differences even within Scandinavia; the incidence and mortality ratio in Denmark is similar to that in the rest of Europe while in Sweden they are intermediate between those of Norway and Denmark. The incidence is even lower in Japan, particularly in women in whom the incidence is reported to be only 0.3 per 100 000 as compared with 1.4 per 100 000 in England and Wales.

It should perhaps be noted that though it is reasonable to assume that cancers of salivary glands, as registered in England and Wales, are carcinomas, this may not be entirely true. Not merely are a few malignant non-epithelial tumours included, but it has certainly happened in the past if not now, that in some centres, pleomorphic adenomas have been included because of obsolete ideas that these tumours were 'semi-malignant'. We have even known cases where Warthin's tumours (adenolymphomas) have been registered as malignant lymphomas. However, such mistakes are probably on a small scale and do not bias the incidence data to a significant degree.

Table 7.1 Percentages of benign and malignant, epithelial salivary gland tumours in different series

<table>
<thead>
<tr>
<th>Sources</th>
<th>Adenomas</th>
<th>Carcinomas</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thackray &amp; Lucas (1974)</td>
<td>83.4%</td>
<td>15.6%</td>
<td>651 (parotid glands only)</td>
</tr>
<tr>
<td>Seifert et al (1986)</td>
<td>74.3%</td>
<td>25.7%</td>
<td>2579</td>
</tr>
<tr>
<td>British Salivary</td>
<td>78.9%</td>
<td>23.1%</td>
<td>3254</td>
</tr>
</tbody>
</table>


The relative frequency of malignant compared with benign salivary gland tumours in different series is shown in Table 7.1 and the site to site variation in Table 7.2. Our data suggest that 23% of salivary gland tumours are malignant whilst in Germany, the figure is almost 26% (Seifert et al, 1986). However, most series agree that the lowest relative frequency of malignant salivary gland tumours compared with benign is in the parotid (15%) and the highest in the sublingual glands (86%), though the overall numbers there were minute. Of the moderate numbers of salivary gland tumours in the minor glands, 46% are likely to
be malignant.

**Classification**

The main classifications have been shown in Chapter 6. There it will be noted that mucoepidermoid and acinic cell tumours were placed in a separate category in the first (1972) WHO classification, from carcinomas. However, they are not (justifiably) termed mucoepidermoid and acinic cell carcinomas and will be discussed with other carcinomas here.

**Table 7.3** Site distribution of different types of 3195 epithelial salivary gland tumours (BSGTP) material

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Parotid</th>
<th>Submandibular</th>
<th>Sublingual</th>
<th>Minor glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types</td>
<td>78.0%</td>
<td>11.0%</td>
<td>0.005%</td>
<td>11.0%</td>
</tr>
<tr>
<td><em>Adenomas</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>61.7%</td>
<td>61.0%</td>
<td>11.1%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Warthin's tumour</td>
<td>14.2%</td>
<td>1.3%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>0.8%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other monomorphic adenomas</td>
<td>7.1%</td>
<td>1.9%</td>
<td>11.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td><em>Carcinomas</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid</td>
<td>1.9%</td>
<td>1.3%</td>
<td>0.0%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Acinic cell</td>
<td>2.7%</td>
<td>0.3%</td>
<td>0.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>1.9%</td>
<td>15.2%</td>
<td>22.2%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Adenocarcinomas (various)</td>
<td>3.2%</td>
<td>4.8%</td>
<td>11.1%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Epidermoid</td>
<td>1.1%</td>
<td>2.2%</td>
<td>0.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>1.6%</td>
<td>4.1%</td>
<td>11.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Carcinoma in pleomorphic adenoma</td>
<td>3.5%</td>
<td>7.6%</td>
<td>33.3%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

**General clinical features**

Malignant salivary gland tumours usually grow more rapidly and, in addition to swelling, frequently cause pain at some stage. Typical features, in the later stages particularly, include fixation, ulceration and involvement of regional lymph nodes. In the parotid gland, facial palsy is a highly significant sign and is likely to imply a poor prognosis. In the series of Seifert *et al* (1986), well-differentiated mucoepidermoid and acinic cell carcinomas never caused facial palsy, but it was present in 40-67% of the more malignant tumours and, in particular, in squamous cell, undifferentiated and solid adenoid cystic carcinomas.

In practice, most malignant salivary gland tumours, unless seen at an unusually late stage, cannot be distinguished from benign tumours.
General management considerations

Overall, only a minority of malignant salivary gland tumours betray their nature clinically and are not recognized until after histology has been carried out. Indeed, many salivary gland cancers present as secondary or tertiary referrals following open biopsy, attempts at enucleation or superficial parotidectomy.

There is usually, therefore, preoperative uncertainty about the best method of management for each individual patient, because of the impossibility of predicting behaviour preoperatively and the absence of any guide that a conventional biopsy might provide. Preoperative fine-needle aspiration cytology followed by frozen-section confirmation during operation may therefore be valuable in suggesting a need for more radical procedures which may lead to the decision to sacrifice the facial nerve and carry out neck dissection. However, where facilities are limited, it may not be possible even to obtain a preoperative frozen section. In such circumstances, as conservative an approach as possible, but consistent with the clinical picture, is appropriate. Alternatively, it may be better for all concerned to refer any patients where the clinical presentation arouses suspicion, to a specialist centre. The literature, in fact, suggests that the number of reoperations and complication rates are less in centres which have specialized in, and have the best facilities for salivary gland surgery.

With regard to the preservation of the facial nerve in patients with malignant tumours but normal facial nerve function preoperatively, it is impossible to lay down hard-and-fast rules. On the one hand, sacrifice of the facial nerve may allow more complete resection and the term 'radical resection' may be interpreted to mean obligatory resection of the facial nerve. However, sacrifice of the facial nerve may not improve the ultimate prognosis. In any case, a patient with a highly malignant tumour may have such a short expectation of life that it becomes difficult to decide whether it is justifiable to add to their disabilities in the time remaining to them.

In recent years, the groundswell of surgical opinion appears to be that a functional facial nerve should be preserved unless found to be involved by tumour. In the cases of tumours merely abutting the facial nerve, it is probably justifiable, despite general oncological principles of surgical clearance, to preserve it and rely on postoperative radiotherapy to control microscopic residual disease.

There is also considerable variation in the interpretation of what constitutes a thorough superficial parotidectomy. The need for reoperation or completion surgery has inevitably to be judged in each individual case from the operative description and the tumour type and margins, as indicated by the histological findings.

Another consideration affecting management is that of the patient's age. Malignant tumours more frequently affect elderly persons and there is often a natural reluctance to operate on someone > 80 years. This reluctance may be justified after clinical investigations and fine-needle aspiration biopsy have shown that the tumour is benign or of low-grade malignancy. In such cases, the tumour may progress so slowly that the patient's expectation and quality of life may be better without any operative interference. By contrast, some patients may not be able to tolerate the idea of having to live with a tumour and their request for surgery should be respected. If this is agreed and the patient is fit for the operation,
surgery should be definitive, not palliative.

Despite such considerations, the behaviour of tumours in some individuals can be so unpredictable that an overenthusiastic surgeon can soon regret having performed a mutilating operation if the patient lives only a few weeks in acute discomfort.

The role of radiotherapy is discussed in relation to individual tumour types below. However, there is no firm evidence that radiotherapy is satisfactory as primary treatment of salivary gland tumours, apart from lymphomas, and for many other types of tumour there is little hard evidence of its value as adjunctive treatment. High success rates have been claimed for neutron beam (cyclotron) therapy, but the numbers of individual types of salivary gland tumours that have been treated have been insignificant and the period of follow-up so short that results are of no statistical value. There is also considerable concern about the severity of the complications and insufficient evidence to indicate that neutron beam therapy offers a better risk:benefit ratio than conventional forms of treatment.

In the end, therefore, we can do no more than suggest guidelines, which are in no way dogmatic, for the management of salivary gland tumours based on our own experience and on a broad survey of the world literature.

**Histogenesis**

All carcinomas arising from salivary glands must broadly be regarded as adenocarcinomas. However, few of them resemble typical adenocarcinomas, like those originating from the gastrointestinal tract, and those categorized as 'adenocarcinoma, not otherwise specified' are rare, as noted by Batsakis *et al.* (1992). Their number has diminished greatly as other entities formerly categorized as adenocarcinomas have been recognized. These workers firmly tie the origin and behaviour of salivary gland carcinomas to different parts of the duct system. Thus they believe that duct carcinomas, papillary and non-papillary adenocarcinomas, high-grade mucoepidermoid carcinomas, squamous carcinomas, oncocytic carcinomas and high-grade carcinoma ex-pleomorphic adenoma are of excretory duct origin. Warthin's tumour, oncocytoma and oncocytic carcinoma, they suggest, arise from striated ducts. The remainder, pleomorphic adenomas, monomorphic adenomas (*sic*), acinic cell carcinomas, adenoid cystic carcinomas, epithelial-myoepithelial carcinomas, terminal duct (polymorphous low grade) adenocarcinomas, low-grade carcinomas ex-pleomorphic adenoma and carcinomas ex monomorphic adenomas, they suggest, arise from intercalated ducts. It is not clear why these workers suggest that oncocytic carcinomas arise from either excretory or striated ducts and hence may fall into the high-grade or benign categories. In any case, little is known of the behaviour of these rare tumours.

**Mucoepidermoid Carcinoma**

Mucoepidermoid carcinomas form 4.8% of all salivary gland tumours in the series of Seifert *et al.* (1986) but only 2.8% in our material. This represents 19.5% and 12%, respectively, of malignant epithelial tumours in these two series. Moreover, the relative frequency of mucoepidermoid carcinomas appears to be considerably greater in the USA and in the series by Foote and Frazell (1954), for example, they formed 11% of all salivary gland tumours and 33% of the malignant tumours. Mucoepidermoid carcinomas have a high relative
frequency in the minor glands where they form between 10 and 15% of all tumours there. The sex incidence is almost equal and the peak age incidence is in the fifth decade.

Mucoepidermoid carcinoma is one of the most common types of post-irradiation salivary gland tumours and in a review of previous reports (including those relating to the survivors of the atomic bombing of Hiroshima and Nagasaki), Watkin and Hobsley (1986) noted that of 70 malignant salivary gland tumours that resulted, 33 (47%) were mucoepidermoid carcinomas which formed the single largest group. Mucoepidermoid carcinomas are also the most frequent type of intraosseous salivary gland tumours as discussed in Chapter 8. Mucoepidermoid carcinoma has also been, apparently uniquely, reported as a second malignant neoplasm by Loy et al (1989), in two children who had had multidrug chemotherapy and cranial irradiation for leukaemia.

**Clinical features**

Well-differentiated mucoepidermoid carcinomas are likely only to give rise to painless swelling and cannot be distinguished from adenomas. As mentioned earlier, they did not cause facial palsy in the series of either Foote and Frazell (1953) or of Seifert et al (1986), but the latter record that 20% of high-grade tumours caused facial palsy and other signs or symptoms typical of carcinomas.

**Macroscopic and microscopic features**

The gross appearances are likely to vary with the grade by in general, mucoepidermoid carcinomas form irregular, poorly circumscribed masses. Unlike most other salivary gland tumours, cyst formation is common, usually as several small cysts, but occasionally as a single large cyst. The cyst contents are typically clear or mucoid unless there has been bleeding.

The distinctive microscopic feature of mucoepidermoid carcinomas is, as the name implies, the juxtaposition of both mucous and epidermoid cells and usually, multiple microcysts (Fig. 7.1).

The mucous cells are large and pale, with a cytoplasm having a frosted-glass appearance. They have a well-defined cell membrane and vary in shape from rounded polygonal to columnar, and form small solid masses or line cysts (Fig. 7.2). Their numbers vary widely but in predominantly solid tumours, are heavily outnumbered by epidermoid cells. Their mucin content is confirmed by using such stains as mucicarmine, which are useful when mucous cells, which contain only minute droplets of mucin, are not otherwise recognizable (Fig. 7.3). This particularly applies to solid or poorly differentiated tumours.

Mucin also fills the cysts, which may burst to release mucin into the surrounding tissues. The released mucin excites an inflammatory and sometimes, a granulomatous reaction. These cysts vary in size from microscopic to gross and occasionally the tumour forms only a mural thickening in a single large cyst.
The epidermoid cells can usually be seen to have intercellular bridges and are mostly in solid masses (Fig. 7.4). Occasionally there may also be keratin and, rarely, cell nest formation. However, Batsakis and Luna (1990) consider that these latter features, if prominent, cast doubt on the diagnosis as they consider that the epidermoid cells are not true squamous cells.

Other cells sometimes present, usually in small numbers, are small, dark, intermediate cells which can form a basal layer to the cyst-lining epithelium. Oncocyte-like cells may also be seen (Fig. 7.5) and these may undergo change into clear cells (Figs 7.6 and 7.7). Clear cells may then form a major part of the tumour, as discussed later with other clear-cell tumours. Aufdemorte et al (1985) have also noted melanin pigmentation in a mucoepidermoid carcinomas of a minor gland but this appears to be an exceptionally unusual finding.

Poorly differentiated mucoepidermoid carcinomas, as mentioned earlier, are frequently solid and may appear to be purely epidermoid unless small droplets of mucin can be demonstrated in some of the cells by appropriate stains (Fig. 7.8). Also, gross nuclear pleomorphism, with giant hyperchromatic nuclei (Fig. 7.9), is common and mitotic activity is more frequent (Fig. 7.10). These tumour cells form broad strands, clearly demarcated from the fibrous stroma in which inflammatory infiltrate is usually scanty. Perineural (Fig. 7.11) or intravascular invasion may be seen and suggests a poor prognosis. High-grade tumours may also show areas of necrosis (Fig. 7.12); this was present in 13% of 89 tumours analyzed by us, and all either recurred or caused the death of the patient.

An intermediate grade can sometimes be distinguished and is characterized by predominance of epidermoid or intermediate cells, a solid pattern of growth with relatively little mucin production, and slight-to-moderate pleomorphism with few mitoses.

The stroma consists of fibrous connective tissue and lack myxochondroid differentiation. Focal inflammatory infiltrates, or foreign-body reactions round cholesterol clefts or extravasated mucus may be seen (Fig. 7.13). Rarely, fibrosis and hyalinization are so extensive that the tumour becomes sclerotic (Fig. 7.14). Chan and Saw (1987), in their report of a sclerotic mucoepidermoid carcinoma, were unable to find any earlier recorded examples. However, Batsakis and Luna (1990) mention stromal desmoplasia as a feature of high-grade mucoepidermoid carcinomas.

**Behaviour, grading and prognosis**

Spread through the gland is more diffuse than that of pleomorphic adenomas and may be aided, as Thackray and Lucas (1974) have suggested, by extravasation of mucus carrying tumour cells with it (Fig. 7.15). As with other salivary gland tumours, enucleation or inadequate local resection is likely to lead to recurrence and should not be considered as appropriate treatment.

Several attempts have been made to correlate grades of malignancy with behaviour. In general, low-grade (cytologically benign) mucoepidermoid carcinomas, with abundant mucous cells and mucin production, are less aggressive (as suggested by their failure to damage the facial nerve mentioned earlier) but, nevertheless, can sometimes show invasive activity microscopically and can occasionally metastasize. Microscopic invasive activity
should therefore be looked for and reported, as it is the only feature that may suggest a potential for metastasis in a cytologically benign tumours. Even when tumours show neither invasion nor any other adverse microscopic feature, they can occasionally disseminate. However, Seifert et al (1986) recorded that none of the well differentiated mucoepidermoid carcinomas metastasized. Of the poorly differentiated tumours, 50% metastasized to lymph nodes and 25% to more distant sites.

Tumours that may be expected to have a poorer prognosis are those which are predominantly solid and have a preponderance of epidermoid cells. These are thought to have the strongest potential for metastasis and should be treated accordingly. Seifert et al (1986) suggest that their five-year survival rate is only 40%, but by contrast, the five-year survival rate for low-grade mucoepidermoid carcinomas is probably approximately 85%.

A follow-up study by Jensen et al (1988) on 39 mucoepidermoid carcinomas has reported 5-, 10- and 15-year survival rates of 92% for low-grade tumours, 47.4%, 47.4% and 35.5% for intermediate grade, and zero for high-grade tumours.

Analysis, by Hickman et al (1984) of survival rates from reports of several series, adequate in size and relevant data, amounting to a total of 749 cases, suggest that the overall five-year survival rate (taking no account of tumour grade) is 70.7% (95% confidence interval) and the ten-year survival rate is 50.0% (95% confidence interval).

Batsakis and Luna (1990) have suggested detailed criteria for separating mucoepidermoid carcinomas into three grades:

➤ Grade 1 is characterized by macro- and microcysts, daughter cyst proliferation from larger cysts, differentiated mucous and epidermoid cells often in equal proportions, minimal-to-moderate numbers of intermediate cells, minimal or absent pleomorphism and rare mitoses, pools of extravasated mucin with stromal reaction and broad front, often circumscribed invasion.

➤ Grade 2 is characterized by absence of macrocysts, few microcysts, solid nests of cells, preponderance of intermediate cells with or without epidermoid differentiation, sometimes sparse mucin-producing cells, less-conspicuous large duct-cell population, fibrosis separating groups of cells, slight-to-moderate pleomorphism, a few mitoses and more prominent nuclei and nucleoli, well-defined invasive property, lack of circumscripton and peripheral inflammatory reaction.

➤ Grade 3 is predominantly solid and characterized by absence of macrocysts, few differentiated cells, especially mucin-positive cells, considerable pleomorphism, prominent nucleoli and readily found mitoses, obvious invasion of soft-tissue including perineural and intravascular, sometimes with desmoplasia of the stroma round clusters of invasive cells but a less prominent inflammatory reaction. The cell constituents range from poorly differentiated to recognizable epidermoid and intermediate to ductal-type adenocarcinoma with participation of epidermoid and intermediate cells or, it is suggested, the tumour may be predominantly glandular and microcystic.
These proposed criteria, however, have not as yet been correlated with outcome.

Our own multivariate analysis of 89 mucoepidermoid carcinomas (Gleeson et al, unpublished data) was based on fewer microscopic criteria of malignancy, but showed that necrosis was one of the strongest correlates with a poor prognosis. Prominent necrosis was also found to be associated with aggressive behaviour of acinic cell carcinomas by El-Naggar et al (1990). By contrast, we have found that the degree of circumscription and the solid or cystic nature of mucoepidermoid carcinomas bore little relation to their outcome. Otherwise, our findings are consistent with the grading proposed by Batsakis and Luna (1990) and such findings as perineural or intravascular invasion - features that are either clearly present or absent and not dependent on subjective assessment - were useful and reliable guides to prognosis.

Hamper et al (1989b) reviewed the history of ideas about grading mucoepidermoid carcinomas and applied cytophotometric analysis to 46 mucoepidermoid carcinomas. They found that those showing diploid histograms usually had a favourable course while those with atypical histograms had a poor prognosis.

Using immunocytochemistry, flow cytometry and clonal dilution studies Ross et al (1992) concluded that the intermediate cells were reserve cells capable of division and differentiation into squamous or mucous cells. They also showed by xenograft studies that only the intermediate cells were capable of active invasion and that they were present in greater numbers in high-grade tumours.

Previous reports, mentioned earlier, on prognosis relating to grade have been based on simpler microscopic criteria and any agreement is only of a general nature. Objective quantification of the variables within such grading systems is also not possible. It is likely therefore that though broad categories of 'low grade' and 'high grade' would be universally accepted, agreement on what constituted borderline cases would be difficult to obtain. It is also unlikely that precise grading could be made on a frozen section during operation.

**Treatment**

Total conservative parotidectomy (Chapter 9) is the treatment of choice for low-grade mucoepidermoid carcinomas. In a very few cases where a small tumour is localized to the lower pole, it would be reasonable to limit the resection to a superficial parotidectomy. Radical parotidectomy and, where appropriate, sacrifice of the facial nerve or neck dissection or both is required for tumours which are recognized by their clinical manifestations or by frozen section to be high grade, and are usually followed by radiotherapy.

Though some mucoepidermoid carcinomas are radiosensitive, radiotherapy alone is not sufficiently reliably effective. Moreover, since the diagnosis of low-grade mucoepidermoid carcinoma will usually have been made after parotidectomy for an apparently benign tumour, radiotherapy is also unlikely to have been considered as the first line of treatment. Radiotherapy may however be given to supplement radical surgery of high-grade tumours.
Acinic Cell Carcinoma

Acinic cell carcinomas account for about 2% of all salivary gland tumours and approximately 10% of malignant epithelial tumours in both our material and in the Hamburg salivary gland register (Seifert et al, 1986). Over 90% of them are found in the parotid glands, and they account for only 2% of the tumours of the minor glands.

Clinical features

Acinic cell carcinomas affect women at least twice as frequently as men and the peak incidence is between the sixth and eighth decades.

These tumours typically form rounded, well-circumscribed swellings and particularly in their early stages, are indistinguishable clinically from benign tumours. They only occasionally cause pain but poorly differentiated acinic cell carcinomas may sometimes be fixed or cause facial palsy.

Though it is a rare event, acinic cell carcinomas also appear to be more frequently bilateral or to be present in two different glands, than any other carcinoma. Gnepp et al (1989) have found 12 such cases and report two cases of acinic cell carcinoma associated with Warthin's tumours.

Microscopy

Acinic cell carcinomas usually appear circumscribed even though the capsule may be incomplete. The most common and readily recognizable appearances of these tumours are the solid and microcystic types, but several subtypes can be distinguished and description of them illustrates how widely the microscopic appearances of these tumours can vary. However, these variations in the configurations of low-grade tumours are of little value in forecasting their behaviour.

Low-grade tumours

Solid type

In typical examples, the tumour cells are in dense sheets (Fig. 7.16) but usually with scattered small microcysts, which are little larger than the cells and give the field a sieve-like appearance. The tumour cells closely resemble the basophilic, rounded polyhedral cells of serous acini; the cytoplasm is granular, period acid-Schiff-positive and contain zymogen (Fig. 7.17). They are frequently in acinar configurations with basally placed nuclei but there is little or no duct formation (Fig. 7.18) and the microcysts form either by accumulation of dammed up secretion or by rupture of cells and coalescence of intracytoplasmic vacuoles. The stroma is usually inconspicuous but occasionally there are foci or a widespread infiltrate of lymphocytes or fibrous tissue proliferation.
Microcystic type

This has a lattice-like or lacy appearance with both serous-type and more compressed cells (Fig. 7.19). Occasionally the microcysts coalesce to form larger cystic cavities (Fig. 7.20) and some of the cells may be vacuolated. Ellis and Gnepp (1988) have found vacuolated cells in 34% of their material and consider them to be fairly distinctive for acinic cell carcinomas. As well as the acinic cells, smaller, cuboidal intercalated duct cells may be seen. These have amphophilic or weakly eosinophilic cytoplasm and central nuclei. Occasional clear cells and their transition from granular cells may also be seen (Fig. 7.21). Variable numbers of lymphocytes may be present in the stroma and may form a conspicuous feature (Fig. 7.22).

Papillary cystic and follicular types

These are less common. The papillary cystic type is probably formed by coalescence of microcystic spaces leaving strands of tumour cells round vascular cores (Fig. 7.23). Such papillary cystic patterns may form the whole or only part of the tumour. The follicular pattern (Fig. 7.24) usually forms only part of the tumour and is only rarely predominant. It can resemble a thyroid follicular carcinoma, having rounded follicle-like spaces filled with eosinophilic amorphous material and lined by cuboidal cells (Fig. 7.25).

Clear-cell type

Clear cells as mentioned earlier, may be a minor or, rarely, the main feature of acinic cell carcinomas and in the latter case may have to be differentiated from other clear-cell tumours (Fig. 7.26). Another rare finding is that of lamellated, psammoma-like bodies (Fig. 7.27), which may be associated with a fibrous stromal reaction. Yet another variant has uniformly basophilic epithelial cells, typically in an acinar arrangement (Figs 7.28 and 7.29). Their appearance suggests that these cells are mucin-producing, but though they are periodic acid-Schiff-positive, they are negative for specific mucin stains.

High-grade tumours

Most acinic cell carcinomas are well differentiated, but this gives little indication of how they will behave. Occasional examples have a more obviously malignant appearance (Fig. 7.30). These show widespread mitotic activity and pleomorphic cells with large vesiculated nuclei containing prominent nucleoli or undifferentiated areas with, occasionally, foci of necrosis (Fig. 7.31). However, they should still be recognizable by the persistence of some granular cells.

Differential diagnosis

Difficulties mainly arise in the case of papillary cystic, follicular and clear-cell types.

Differentiation of acinic cell carcinomas which are wholly of papillary cystic or follicular from thyroid tumours is, as mentioned earlier, occasionally difficult. Ellis and Gnepp (1988) report that, unexpectedly, acinic cell carcinomas frequently stain positively with mucicarmine but thyroid carcinomas may also contain intracellular mucin (Mlynek et al, 1985). This problem may therefore have to be resolved by immunostaining for thyroglobulin.
or, if this fails, by investigation of the patient for a primary thyroid tumour.

Clear-cell types have to be differentiated from other clear-cell tumours if no granular cells are evident, as discussed later.

Seifert et al (1986) have described variants of acinic cell carcinomas, aspirates of which were rich in lymphocytes and showed partial oncocytic differentiation; they thus resembled Warthin's tumours. However, we have not seen variants with oncocytic differentiation in our material.

**Behaviour and grading**

Even cytologically benign acinic cell carcinomas can be invasive (Figs 7.32 and 7.33) and this behaviour appears to correlate with a potential for local recurrence or more distant spread. Nevertheless, a reasonably good correlation between the degree of differentiation and prognosis has been reported by Evans and Cruikshank (1970), Batsakis et al (1990) and Seifert et al (1986). By contrast, Ellis and Gnepp (1988) in an analysis of 244 cases, found that no one tumour pattern or type was strongly indicative of a poor prognosis. However, they found that infiltrative growth, multinodularity and stromal hyalinization were frequently seen in tumours that recurred or metastasized, and that an intercalated duct-cell type of tumour was slightly more frequent among those which metastasized.

In a further attempt to predict prognosis, Hamper et al (1990a) applied DNA cytometry to 55 acinic cell carcinomas but found no correlation between the DNA content of the tumours and whether they were diploid or near-diploid, and prognosis. In an analysis of the outcome in 40 of these cases, they found that of 12 patients with low-grade tumours, 10 (83.3%) had an unfavourable outcome, 5 (42%) had recurrences and 5 (42%) died from their tumours; of 28 patients with high-grade tumours, 15 (53.6%) had an unfavourable outcome, 12 (42.9%) had recurrences and 7 (25%) died from their tumour. In view of the numbers involved, these figures were not significant except in so far as they showed no difference in outcome in relation to differentiation. By contrast, El-Naggar et al (1990) also applied flow cytometry in a retrospective assessment of 15 acinic cell carcinomas and found that only patients having tumours showing aneuploidy, but none of those with diploid tumours, died or had metastases within a 10-year period. Other features associated with aggressive behaviour were prominent necrosis, tubuloductal differentiation and dedifferentiation areas.

Overall, local recurrence has been reported in 20% of acinic cell carcinomas, metastases to regional lymph nodes in 10% of cases and death from distant metastases in approximately 6%, by Spiro et al (1978), Jack (1981) and Ellis and Corio (1983), respectively. Seifert et al (1986) reported that 36% of well-differentiated tumours had lymph node but no distant metastases, whilst the figures for poorly differentiated tumours were 50% and 27%, respectively.

Ellis and Gnepp (1988) in reviewing 244 cases, found a local recurrence rate of 12%, metastases in 8% and a 6% death rate in a mean period of 8.9 years (range 3 months to 34 years). Retrospective analysis of 101 reported cases with usable data, by Hickman et al (1984) suggested an expected five-year survival rate of 82% and a 10-year survival rate of 68%.
Exceptionally long periods of follow-up were recorded by Lewis et al (1991) in their study of 90 patients. They had been followed for at least 10 years or until death and calculated determinate survival probabilities were 90% at five years, 83% at 10 years and 67% at 20 years.

In the cases analyzed by Lewis et al (1991), the primary treatment group of 63 patients had been followed for up to 45 years; the remainder (27 patients), who had been referred for recurrent disease, were followed-up for a median period of 12 years. Forty-four per cent of the patients had local recurrences, 19% had metastases and 25% died from their disease. Local recurrences first appeared up to 30 years after presentation and death followed up to 38 years later. Clinical features associated with a poor prognosis were pain or fixation, signs of gross invasion and local excision rather than parotidectomy. Microscopic features associated with a poor prognosis were a desmoplastic stromal reaction, atypia or increased mitotic activity.

**Treatment**

In view of the uncertainty about the prognostic value of the histological findings, even well-differentiated acinic cell carcinomas should be treated by total conservative parotidectomy with preservation of the facial nerve whenever possible. However, if the tumour has to be peeled off and is therefore intimately related to the nerve, it should be sacrificed. Poorly differentiated tumours, with preoperative facial weakness, should be treated by radical parotidectomy followed by radiotherapy.

**Adenoid Cystic Carcinoma ('Cylindroma')**

Adenoid cystic carcinomas formed 5% of 3500 epithelial salivary gland tumours in our material, and 23% of the carcinomas. They comprised 28% of parotid salivary gland tumours but had a much higher relative frequency in the submandibular and minor glands where, overall, > 70% of adenoid cystic carcinomas were found. The palate is by far the most frequent site in minor glands.

**Clinical features**

The peak age incidence is in the sixth decade (range 12-72 years) and the female-to-male ratio is 1.3.

In most cases, the tumour is slow growing and this slow rate of growth is mirrored by the late appearance of recurrences. Nevertheless, adenoid cystic carcinoma frequently causes pain as a result of its well-known propensity for infiltration of nerves. It should be noted that pain in the distribution of one or several cranial nerves can be caused by an occult adenoid cystic carcinoma which may elude diagnosis for a considerable period. Malins and Farrow (1991), for example, describe facial pain lasting for 18 months and 7 years respectively before the causative adenoid cystic carcinomas were detected. In the first case, the tumour was 1.5 cm and in the second, 1 cm in diameter. The difficulty in finding some adenoid cystic carcinomas is enhanced by their predilection for arising in minor glands which extend as far back as the pharynx.
Facial palsy is another common manifestation of their invasiveness and Seifert et al. (1986) quote a frequency of facial palsy in 20%, 40% and 65% for the cribriform, tubular and solid types, respectively.

**Microscopic features**

There are several variants of which the cribriform is the single most common type and the most readily recognizable. However, it is important to note that although many adenoid cystic carcinomas are instantly recognizable, there can be wide variation between the appearance of individual fields, of which some can look deceptively benign.

**Cribriform type**

In typical cribriform adenoid cystic carcinomas, the cells are small and darkly staining with little cytoplasm (Fig. 7.34). Usually they form oval islands of cells containing many microcystic spaces which are more often surrounded by myoepithelial than duct-lining cells (Fig. 7.35). There are also duct-like structures which have a double-layered wall of duct-lining cells surrounded by an outer layer of myoepithelial cells; they usually contain PAS positive material (Fig. 7.36). However, these duct-like structures are rarely seen cut longitudinally.

The stroma is fibrous and contains elastic fibres. Formation of basophilic hyaline material by myoepithelial cells is also sometimes prominent (Fig. 7.37). This material frequently surrounds the epithelial cells as a thick band, may form the major component of the stroma and also fills the cribriform spaces (Fig. 7.38).

As with other subtypes of adenoid cystic carcinoma, perineural and sometimes intraneural spread may be conspicuous.

**Hyaline type**

Overproduction of hyaline material can lead to such distension of the cyst-like spaces and attenuation of the cells as to give a lace-like appearance (Figs 7.39 and 7.40), or it may break up the tumour pattern completely, leaving only thin strands of cells forming incomplete outlines to coalescing globules of hyaline material. Less often, formation of hyaline material is restricted within small groups of cells, so that a reticular or lattice-like appearance is produced. A somewhat similar appearance may be seen in parts of pleomorphic adenomas as shown earlier, and can cause diagnostic confusion. In extreme cases, so much hyaline material is formed that the tumour pattern is totally destroyed and only minute clamps of cells or single duct-like structures are scattered in a sea of mucoid or hyaline material (Fig. 7.41).

**Tubular type**

These form only 20-30% of adenoid cystic carcinomas and as the name implies, consist of small, dark, epithelial cells forming cords (Fig. 7.42) or duct-like structures with multilayered walls (Fig. 7.43), sometimes with an outer clear-cell layer, and surrounded by a hyaline stroma. Excessive hyalinization of the stroma in this variant can lead to disintegration of the cellular architecture (Fig. 7.44).
Solid (basaloid) type

Solid areas may be seen in addition to cribriform. Alternatively, they may occasionally predominate (Fig. 7.45) but are usually distinguishable from other small-cell carcinomas by the presence of sparse duct-like spaces or small foci of necrosis within the solid masses (Fig. 7.46). Mitotic activity is greater in the solid than other types of adenoid cystic carcinoma.

Behaviour and prognosis

Though usually slow growing, adenoid cystic carcinoma is invasive and infiltrative, and perineural spread is characteristic of, though by no means exclusive, to this tumour (Figs 7.47 and 7.48). Other important routes are bony canals, either those of haversian systems or those conveying arteries, and marrow spaces, nerves or other structures. The tumour can spread far into a bone by these routes, with relatively little bone destruction (Fig. 7.49) or radiographic evidence of its true extent. Alternatively, it may proliferate, with extensive bone destruction once well within the tissue.

Metastases are usually late events and in most cases follow multiple recurrences. In many cases, lymph-node involvement is due to invasion by contiguous tumour rather than by lymphatic permeation or embolization (Fig. 7.50), hence the apparently anomalous finding of Seifert et al (1986) that distant metastases were considerably more frequently found than spread to the lymph nodes. Blood-borne metastases are mainly to the lungs or liver. However, secondary deposits retain the slow-growing character of the primary tumour. They frequently permit survival for many years and success has also been claimed for excision of isolated secondary deposits.

As noted earlier, pain is sometimes the first symptom and can long precede the discovery of an occult adenoid cystic carcinoma.

Grading

Seifert et al (1986) noted that lymph-node metastases were seen in none of the tubular, 4% of the cribriform and 33% of the solid types. Distant metastases were found in 36%, 58% and 67%, respectively. In a study of 19 cases, Santucci and Bondi (1989) concluded that the number of cystic spaces per square millimetre correlated well with the disease-free period or survival, within periods of follow-up up to 52 months after treatment.

Hamper et al (1990b) applied DNA cytometry and other criteria to 90 adenoid cystic carcinomas to assess the prognostic value of various features. Cytophotometry showed that diploid histograms were associated with the longest (median 128 months) survivals and atypical histograms with the shortest (median 65 months). Other unfavourable features were solid-type histology and tumour size (> 4 cm in diameter).

Because of their slow rate of growth, the prognosis of adenoid cystic carcinoma is considerably better than for adenocarcinomas, particularly in the short term. Analysis of reports of a total of 1065 adenoid cystic carcinomas (Hickman et al, 1984) suggested five-and ten-year survival rates of 62.4% and 38.9%, respectively. This compares with the five- and twelve-year survival rates of 73% and 39% reported by Blanck et al (1967) for 35 cases,
and of 76% and 33% obtained by Seifert et al (1986).

**Treatment**

The infiltrative growth pattern, the potential for spread along nerves and bony canals and the deterioration of prognosis with recurrences, presents a dilemma for any surgeon anxious to avoid a mutilating operation. Unfortunately, there is as yet no consensus as to the optimal approach nor any firm evidence that postoperative radiation improves the prognosis. However, it is generally accepted that radiotherapy improves local control and should therefore be considered for every patient with an adenoid cystic carcinoma.

Seifert et al (1986) suggest that for tumours ≤ 2.5 cm in size, comprehensive (supraradical) surgery is indicated. This comprises radical parotidectomy, sacrifice of the facial nerve and resection of surrounding tissues, including the mandible, maxillary tuberosities, mastoid process or temporal bone, and contents of the infratemporal fossa, to provide a wide margin of healthy tissue. Though an arbitrary figure has been given for the maximum size of tumour where supraradical surgery can be contemplated, much may depend on other factors such as the patient's age, attitude and general health. In the young otherwise healthy patient, supraradical surgery may be considered for larger tumours, in view of the greater potential expectation of life.

For those with more extensive disease, there is no certainty that wide excision with tumour-free margins can ever be obtained, so that it seems difficult to justify the functional and cosmetic deficits resulting from such procedures. Excision is therefore limited to radical parotidectomy with sacrifice of the facial nerve (to remove a possible path of spread of residual tumour) and, possibly, postoperative radiotherapy. As mentioned earlier it appears that a metastasis can sometimes be removed with beneficial effects on the outcome.

It is, nevertheless, still surprising that the more radical surgery of the Götingen group (Seifert et al, 1986) gave no better results than the much earlier cases of Blanck et al (1967) where parotidectomy was carried out in only 3 of 35 cases and in 31 only local excision was performed. Indeed, Seifert et al (1986) admit that, despite their recommendation of supraradical surgery even for small tumours, the method of treatment had very little influence on the outcome and that they could not confirm any prolongation of survival as a result of giving radiotherapy.

**Polymorphous Low-Grade Adenocarcinoma**

The relatively recent recognition of this entity has meant that there is some variation in the terminology and, for example, the terms, lobular and 'terminal' duct carcinoma have also been applied to it. Alternatively some of these terms may represent subgroups of these tumours, which have a wide spectrum of appearances. However, the term 'polymorphous low-grade adenocarcinoma' describes the most striking feature of its appearances and, despite an infiltrative pattern of growth, the low potential for metastasis over periods of many years.
Clinical aspects

So far, > 200 cases have been reported. Most have been tumours of the minor glands with the palate as the site of predilection, but with some cases in the buccal mucosa, retromolar area, lip and tongue. Only four examples in the parotid gland have been reported, with one reported by Ritland et al (1993). Vincent et al (1994) evaluated 204 cases including 15 of their own and analyzed the sites of 173 tumours; 87 of them had arisen in the palate. Patients are mostly between 50 and 75 years, the mean age being 65 years; women may be slightly more frequently affected.

The clinical features of these tumours are usually nondescript in that they form firm painless swellings but may later ulcerate.

Microscopy

In contrast to the variety of microscopic architectural patterns produced by this tumour, there is cytological uniformity with bland-appearing nuclei. The latter are pale and ovoid with a finely speckled pattern of chromatin and small or inconspicuous nucleoli. The cytoplasm is usually scanty but more columnar cells may surround some of the cell masses.

The main microscopic patterns include:

➤ Solid (lobular) masses of cells surrounded by fibrous tissue (Fig. 7.51).

➤ Cribriform areas (Fig. 7.52).

➤ Duct-like structures with mucinous or hyaline stroma and hyaline material present in the spaces in the cribriform areas.

➤ Strands or fascicles of cells sometimes in concentric arrangements (Fig. 7.53).

➤ Papillary structures or a papillary cystic pattern (Fig. 7.54).

Fibrous bands between different areas of the tumour are sometimes conspicuous (Fig. 7.55). The concentric arrangements of cells, to which the term 'targetoid' has been applied, sometimes surround nerve fibrils or blood vessels, or may form a solid whorl of uniform tumour cells (Figs 7.56 and 7.57).

In 22 polymorphous low-grade adenocarcinomas, Slootweg (1993) analyzed the frequency of lobular, papillary cystic, trabecular-tubular and cribriform configurations. The last was the least common (6 of 22), lobular and papillary cystic patterns were present in the great majority and 50% showed trabecular-tubular configurations. By contrast, papillary cystic patterns were infrequent in metastases and there was a clear distinction between these tumours and papillary cystic adenocarcinomas.
Perineural invasion and, despite partial circumscription by fibrous tissue, infiltration of surrounding structures by strands of tumour cells can be seen. Nevertheless, unlike more malignant neoplasms, substantial amounts of normal salivary gland tissue and fat can persist in the depths of the tumour (Fig. 7.58).

If the term 'terminal duct carcinoma', is used, it implies the presence of tubules, cut transversely or obliquely. These cells have distinctly visible cytoplasm and resemble intercalated duct cells. The overall pattern may therefore resemble that of a tubular adenoma or the tubular variant of adenoid cystic carcinoma. Solid masses of tumour cells may also project into and largely fill enlarged duct spaces. However, the term 'terminal duct carcinoma' is unhelpful in that it is questionable whether terminal ducts are recognizable as an anatomical entity and, as already mentioned, the tubules seen in some of these tumours resemble intercalated ducts, where indeed Batsakis et al (1992) believe they originate.

Reported electron microscopic findings include true glandular structures with luminal junctional complexes and microvilli projecting into lumens containing homogeneous material. Myoepithelial cells were not identified. In addition, there were pseudoglandular spaces with a smooth lining of basement membrane lacking well-defined junctional complexes near the luminal surfaces.

An incidental finding is that tyrosine-rich crystaloids may be widespread in the stroma.

Four cases were reported by Gnepp et al (1988) who reviewed the histopathology and carried out immunohistochemistry on this material. In summary, they suggest that where extensive cribriform areas and perineural invasion in a polymorphous low-grade adenocarcinoma cause difficulties in diagnosis, it can be distinguished from adenoid cystic carcinoma particularly by the staining of > 90% of polymorphous low-grade adenocarcinoma tumour cells with EMA. By contrast, EMA stained only the true luminal cells of adenoid cystic carcinomas. Carcinoembryonic antigen (CEA) staining was positive for only 5-15% of cells, and both muscle-specific actin and CEA staining were usually negative in cribriform areas of polymorphous adenocarcinomas. Vincent et al (1994) therefore concluded that the histological features rather than special stains were more useful for differentiating polymorphous low-grade adenocarcinomas from other tumours. However, they also noted the frequency with which many cases of polymorphous low-grade adenocarcinomas had been misdiagnosed, most frequently as monomorphic adenomas or adenoid cystic carcinomas.

**Behaviour and prognosis**

As mentioned earlier, these tumours are infiltrative and locally invasive but as far as can be determined, rarely metastasize. Admittedly the numbers reported have been small and there are few cases which have been followed for prolonged periods. But of those that have been followed for periods up to 20 years, distant metastases have not been recorded.

Vincent et al (1994) found an overall recurrence rate of 17% for 116 cases where follow-up information was available. These appeared from 1 to 19 years after initial treatment. These workers suggested that polymorphous low-grade adenocarcinomas having a predominantly papillary configuration should be categorized as papillary cystadenocarcinomas since the latter have a stronger tendency to metastasize, as described earlier.
Treatment

Despite the relatively benign nature of this tumour, local recurrence has been frequent among the reported cases, but in some of these at least, the resection margins had not been adequate or the tumours had been misdiagnosed as benign. Excision should therefore be as radical as possible to obtain a good surgical clearance. In view of the usual sites for these tumours, both early recognition and complete excision without significant complications should be possible.

Epithelial-Myoepithelial (Intercalated Duct) Carcinoma

This tumour was originally described by Donath and Seifert (1972) and since then has been described in detail by Corio et al (1982); approximately 40 cases have been reported. A similar example was shown as the last of a series of so-called 'duct carcinomas' reported by Kleinsasser et al (1968), but salivary duct carcinomas are now categorized as a separate group as described later.

Clinical features

The mean age of affected patients appears to be about 60 years and the peak age incidence of the tumour is in the seventh and eighth decades although occasional examples have been in young adults. Women have been predominantly affected in the ratio of 2:1.

Over 80% of these tumours have been in the parotid glands. The majority have given rise to otherwise asymptomatic swellings, but a minority have caused pain or facial weakness.

Microscopy

The tumour is typically multinodular and though it appears circumscribed, like pleomorphic adenomas, the capsule may be thick in part, incomplete or have tumour nodules extending through it.

Duct-like structures or larger spaces are characteristically present. Alternatively, such structures may be absent and the cells are predominantly in an organoid (thecal) pattern with a well-defined basal membrane.

The cells are characteristically of two types, namely small dark cells lining the duct-like spaces, and large glass-clear cells which surround the dark cells and usually predominate (Fig. 7.59). The dark cells are usually roughly cuboidal, eosinophilic and have little cytoplasm. The clear cells are considerably larger, of rounded polyhedral shape and can usually be shown by periodic acid-Schiff staining to contain glycogen, but are mucicarmine-negative (Fig. 7.60). In some areas of these tumours, there may be solid sheets of clear cells without any distinguishing features (Fig. 7.61).

The lumens of the duct-like or larger spaces sometimes contain eosinophilic periodic acid-Schiff-positive material. The basal membrane surrounding the organoid nests of tumour cells also stains positive, and may be considerably thickened and hyaline in appearance.
In some cases, there are cyst-like spaces into which there are papillary projections of tumour cells and there is thus a variety of patterns and of numbers of clear cells in individual tumours or within a single example.

Electron microscopy has confirmed that the dark cells are epithelial and that the clear cells are myoepithelial in that the cytoplasm contains myofilaments, pinocytic granules, glycogen and lipofuscin. The small, dark cells by contrast are ductal epithelium with microvilli on some points on the luminal surface. They contain tonofilaments and are joined by desmosomes.

Immunohistochemistry has confirmed that the clear cells are strongly S-100 protein and myosin positive but have variable keratin reactions. This seems, therefore, to be a useful means of confirming the myoepithelial nature of clear cells in epithelial-myoepithelial carcinomas here clear cells are overwhelmingly predominant. Though neoplastic myoepithelial cells may become S-100 positive, the long held belief that normal myoepithelial cells were S-100-positive appears now to be questionable. Assumptions about the histogenesis of salivary gland tumours such as epithelial-myoepithelial carcinomas may possibly therefore have to be reassessed.

**Behaviour and prognosis**

Mitoses are rarely seen, but the potential of epithelia-myoepithelial carcinomas for invasion is shown by the occasional finding of perineural infiltration or intravascular growth (Fig. 7.62). Not surprisingly, these tumours have recurred in a significant number of reported cases (13 of 37). Two patients have died with metastases which have been in lymphnodes, lung and kidney. Seifert et al (1986) suggest that five-year survival rate is 65%.

**Treatment**

Although often regarded as of low-grade malignancy, the behaviour of reported cases suggests that total conservative or radical parotidectomy should be carried out. The latter is appropriate particularly if there is preoperative facial weakness. In the case of other glands, *en bloc* resection should be carried out.

**Clear-Cell Tumours**

Clear cells can be seen in a variety of salivary gland tumours, but are frequently few in number. It is apparent that there is no single entity that can be categorized as a clear-cell tumour and clear-cell formation can result from a variety of processes. These include sparsity of organelles, intracytoplasmic accumulation of materials such as glycogen, mucus, lipids or clear secretory granules, or hydropic change or fixation artifact.

It is also doubtful whether there is any such entity as a clear-cell adenoma. Many, such as Batsakis (1980), believe that all clear-cell tumours should be regarded as low-grade carcinomas and this view is supported by Ellis and Gnepp (1988). Nevertheless, the latter, like most other workers, include the clear-cell variant of oncocytoma, among the clear-cell tumours.
Varieties of clear-cell tumours

A variety of clear-cell tumours is, therefore, described here to give an adequate picture of the present state of knowledge. However, it must be admitted that some clear-cell tumours remain difficult to fit into any of the recognized categories.

Clear-cell onc cytoma

This is a rare variant of a rare tumour and its name is something of an internal contradiction.

The characteristics of oncocytomas have been described earlier but, exceptionally, in these tumours there can be transition from typical oncocytes to clear cells, which on even fewer occasions form a high proportion or the major component. The tumour then appears as a circumscribed mass of rounded polyhedral clear cells, with small, dark eccentric nuclei, arranged in an organoid pattern and surrounded by thin fibrous septa (Fig. 7.63). As noted in Chapter 6, clear cells are most frequently found in multinodular oncocytic hyperplasia and in associated oncocytomas.

While a high proportion of cells of an oncocytoma can thus be glass-clear, at least a few cells remain eosinophilic, contain a small amount of eosinophilic material or appear granular.

Staining of these clear cells with PTAH, which should be taken up by the many mitochondria of oncocytes, is sometimes unreliable. However, PTAH staining is sometimes intense and includes the oncocytic duct cells of adjacent normal salivary tissue. Periodic acid-Schiff staining may show variable amounts of glycogen, but mucicarmine staining is negative. Ellis and Gnepp (1988) suggest that the appearance of the clear cells in oncocytomas is largely due to fixation artifact. This seems to be confirmed by electron microscopy which shows many of these cells to lack any organelles or to have only swollen mitochondria limited to the periphery of the cells. Similar clear-cell transformation may also be rarely seen in oncocytosis. However, Davy et al (1994) have shown by electron microscopy that the cytoplasm of these clear cells is occupied by glycogen with margination of the chromatin and organelles.

Unlike other clear-cell tumours, the clear-cell variant of oncocytoma appears to be benign.

Mucoepidermoid and acinic cell carcinoma

These tumours sometimes contain foci of glass-clear cells or rarely, such cells predominate. However, closer examination of the material should establish these tumours as mucoepidermoid (see Fig. 7) or acinic cell carcinomas (see Fig. 7.26) as the case may be. According to Ellis and Gnepp (1988) clear cells appearing in acinic cell carcinomas are fixation artifacts, while the clear cells found in mucoepidermoid carcinomas sometimes contain glycogen but only rarely mucin.
Such tumours are not normally therefore categorized as clear-cell tumours but merely variants of well-recognized neoplasms.

**Epithelial-myoepithelial carcinoma**

This tumour, the main type of clear-cell tumour, has been described earlier (see Fig. 7.64).

**Sebaceous carcinoma**

Occasionally one of these rare tumours consists largely of clear rather than foamy cells, but in such cases the characteristic lobular configuration may assist in making the diagnosis (Fig. 7.65).

**Metastatic renal cell carcinoma (hypernephroma)**

When clinical or any other features suggest that a clear-cell tumour of a salivary gland is a secondary deposit, the kidney is the only important source. The other possible source of a secondary deposit, in a salivary gland, of a clear-cell tumour is a parathyroid carcinoma with *wasserhelle* (water-clear) cells, but this appears to be no more than a theoretical hazard.

In the case of a renal cell carcinoma, difficulties arise because metastases are frequently its first sign and renal disease is unsuspected. The 'classical' triad of gross haematuria, pain in the loin and a renal mass is late in appearance and present in only 10% of patients. However, microscopic haematuria alone can be found in 60% of patients and about 50% of patients have non-specific systemic symptoms such as fever, fatigue or loss of weight.

**Microscopy**

Renal cell carcinoma consists of solid groups of clear cells with small eccentric nuclei in an organoid or trabecular arrangement (Figs 7.66 and 7.67). The blood vessels are typically dilated and form scattered sinusoids; foci of haemorrhage and deposits of haemosiderin may be seen. Granular cells may also be present and in some cases predominate.

The clear cells are usually uniform size and show little or no atypia but those which show nuclear and cellular pleomorphism, and mitotic activity are less likely to be confused with primary salivary gland tumours.

Differentiation from epithelial-myoepithelial salivary gland tumours can be difficult. Ellis and Gnepp (1988) suggest that a helpful distinguishing feature of epithelial-myoepithelial carcinoma is that small blood vessels can be seen running between the groups of tumour cells, but there are typically large sinusoids in renal cell carcinomas. In addition, if unblocked material is available, the demonstration of abundant fat is typical of renal cell carcinomas but unfortunately, is not invariably present. Glycogen is common to both epithelial-myoepithelial and real cell carcinomas.
If doubt remains, intravenous urography and if necessary a computerized tomography or ultrasound scan need to be carried out. If a renal cell carcinoma is present, a salivary gland metastasis is likely to mean that the prognosis is poor. However, some of these tumours grow unexpectedly slowly and removal of both the primary tumour and metastasis has occasionally resulted in a cure.

**Hyalinizing Clear-Cell Carcinoma of Salivary Gland**

Milchgrub et al (1994) have presented 11 cases of yet another type of clear-cell carcinoma of salivary glands in which the epithelium was surrounded by hyalinized bands with foci of myxohyaline stroma. Despite some microscopic resemblances to epithelial-myoepithelial carcinoma, immunohistochemistry and electron microscopy failed to show myoepithelial cells. They noted four earlier examples which had been illustrated but not characterized as a distinct entity.

The patients comprised eight females and three males. Ages ranged from 34 to 78 years with a mean of 55 years. Minor salivary glands were most frequently affected (nine cases). There was a single case in the parotid gland and another in the larynx.

**Microscopy**

The tumour cells formed trabeculae, cords or nests and infiltrated any residual acini or other soft tissues such as the overlying oral mucosa. They were mostly round to polygonal with clear, periodic acid-Schiff-positive cytoplasm and central nuclei. The nuclear membranes frequently appeared indented with a suggestion of lobulation. Mitotic activity was noted in only two cases. In 10 of the 11 cases reported by Milchgrub et al (1994), there were polygonal cells with eosinophilic granular cytoplasm mingling with the clear cells and appeared to represent transition between the two types.

The tumour cells were immunoreactive for low- and high-molecular weight keratins and epithelial membrane antigen. In two cases there was CEA reactivity. Immunoreactivity for S-100 protein, smooth muscle actin and muscle-specific actin was consistently negative. Electron microscopy failed to show any cells with myoepithelial differentiation, zymogen, mucin or dense core neurosecretory granules.

A distinctive feature was the stroma which was desmoplastic in both the primary tumours and metastasis. It sharply outlined the trabeculae and nests of tumour cells and enhanced the streaming effect where the tumour cells were aligned in slender cords. In five cases, the stroma was hyalinized and periodic acid-Schiff-positive and, though resembling amyloid, was Congo red-negative. In eight tumours there were also foci of loose myxoid stroma. Perineural invasion was seen in most cases but vascular invasion was absent. Electron microscopy showed a prominent continuous layer of basal lamina surrounding most tumour cell nests.

Eight of the eleven tumours reported by Milchgrub et al (1994) had originally been reported as other types of carcinomas such as poorly differentiated adenocarcinoma, epithelial-myoepithelial carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, squamous cell carcinoma, carcinoma in pleomorphic adenoma or calcifying epithelial odontogenic tumour.
Behaviour and management

One of the patients reported by Milchgrub et al. (1994) presented with cervical nodal metastases but no metastases developed in the remaining nine cases. Clinical follow-up ranged in duration from 6 months to 11 years with no evidence of recurrent disease in any of the patients. Hyalinizing clear-cell carcinoma therefore appears to be of low-grade malignancy and wide excision possibly supplemented by radiotherapy appears to be the treatment of choice.

Salivary Duct Carcinoma (Excretory or Large Duct Carcinoma)

These tumours were originally described by Kleinsasser et al. (1968) who termed them 'duct carcinomas' because of their histological resemblance to duct carcinomas of the breast. Nevertheless, probably only two of the five cases that he presented can be regarded as duct carcinoma in its present connotation. Also the term, 'duct carcinoma' might cause confusion with several other types of salivary gland carcinomas which also arise from duct cells and in particular, with what has been termed 'terminal duct carcinoma' (low-grade polymorphous adenocarcinoma) and the 'intercalated duct carcinoma' (epithelial-myoepithelial carcinoma). Moreover, Seifert et al. (1986) use the term 'duct carcinoma' for the epithelial-myoepithelial carcinoma.

Any confusion caused by the different terminologies is particularly unfortunate in that duct carcinomas, as described here, are significantly more aggressive than other salivary duct carcinomas. To resolve these difficulties the term 'excretory (large) duct carcinomas' was coined, and Chen and Hafez (1981) found reports of 12 acceptable examples. Eleven of these arose from Stenson's duct and one from the excretory duct of a minor salivary gland in the palate. Luna et al. (1987) described 30 cases and Afzelius et al. (1987) reported another 12. Six more cases have been reported by Simpson et al. (1991) from among 212 parotid gland tumours seen in a 12-year period. The incidence of these tumours is therefore likely to be greater than previously suspected. Overall however, Barnes et al. (1994) believed that few more than a hundred cases had been reported in the English-language literature.

Clinical features

In reviewing 104 cases including their own, Barnes et al. (1994) concluded that duct carcinomas affected major salivary glands, particularly the parotids, in 96% of cases, were three times as common in males as in females, and affected patients > 50 years (range 22-91 years). Growth is typically rapid and may be associated with pain or facial palsy. The cervical lymph nodes may be involved at the time of presentation.

Microscopy

Four patterns, namely, papillary, cribriform, solid and a rare comedo type, may be seen (Figs 7.68 and 7.69). The tumour is actively invasive. The cells are moderately large with eosinophilic cytoplasm and may contain periodic acid-Schiff-positive granules but are mucicarmine-negative. The nuclei are large, hyperchromatic and pleomorphic, with prominent nucleoli, and mitoses are frequent.
The tumour cells form nodular masses in a fibrovascular stroma in which there may be small amounts of mucin and a light inflammatory infiltrate. The stroma may show areas of eosinophilic hyalinization. Perineural and intraneural invasion is relatively frequent. Vascular invasion and intralymphatic emboli may also be seen. Cribriform and papillary cystic patterns may sometimes be seen in adjacent nodules. The comedo type is characterized by extensive central necrosis within duct-like structures as in comedo carcinoma of the breast but other areas of necrosis are also common. Duct carcinomas of salivary glands may induce dense fibrosis like scirrhus-duct carcinomas of the breast.

Delgado et al (1993) reviewed the immunocytochemistry, electron microscopy and results of treatment of 15 duct carcinomas of which three had arisen in pleomorphic adenomas. Men were affected in the ratio of 4:1. All 15 tumours stained positively for one or more of five commercially available 'breast-specific' markers but oestrogen receptor stains were uniformly negative in 11 that were tested.

**Behaviour and prognosis**

As mentioned earlier, the growth of duct carcinomas is typically rapid and aggressive. The tumour is infiltrative and lacks clearly defined boundaries. Variations in the microscopic appearances to not appear to correlate with the behaviour sufficiently well to be of predictive value, except insofar as the comedo type may have the worst prognosis. However, Simpson et al (1991) noted that there was little difference in the survival times of patients with tumours showing less well-defined areas of necrosis than the comedo type and that the longest survival was in a patient whose tumour showed no necrosis.

Nine of 12 cases reported by Chen and Hafez (1981) developed metastases and eight died. Of the three remaining patients, only one had remained free of recurrence after six years. Of the six patients reported by Simpson et al (1991), all died within 6-28 months except one who was alive after 68 months, but who also had metastases.

Despite total or radical parotidectomy, radical neck dissection and/or radiotherapy in the majority of cases, only three of the 15 patients reported by Delgado et al (1993) were alive and without disease after 2-5 years. Unexpectedly, two of these three patients had tumours with intraductal growth patterns and comedo-like necrosis. One had arisen in a pleomorphic adenoma but unlike most of the 12 other cases, none of them had lymph-node metastases.

In their analysis of 104 cases, Barnes et al (1994) found that one-third of patients experienced local recurrences, 59% experienced regional nodal spread and 49% developed distant metastases particularly to lungs and bone. Sixty-five per cent of these patients died from their disease usually within four years, but all of those with distant metastases died. Tumour ploidy as determined in 12 of their 13 cases appeared to have little prognostic significance.

**Treatment**

In view of reported behaviour of this tumour, radical treatment appears to be necessary in the hope of improving the chances of survival. Supplementary irradiation is frequently
given but its value is uncertain.

Radical parotidectomy or *en bloc* resection of other salivary glands when feasible, appears to be the treatment of choice. Neck dissection even when there is no clinical involvement of nodes may be indicated. Though Seifert et al (1986) reported a five-year survival rate of 65% with such treatment, their criteria for definition of duct carcinoma are in doubt and more recent reports suggest that ≤70% of patients may die within three years.

**Basal Cell (Basaloid) Adenocarcinoma**

Twenty-one cases of basal cell adenocarcinomas were described by Ellis and Gnepp (1988) who considered them to be malignant counterparts of, and sometimes difficult to distinguish histologically from, basal cell adenomas, particularly the membranous variant. One of these tumours caused facial pain and another, facial palsy. Twenty-nine cases have been reviewed by Ellis and Wiscovitch (1990). However, illustrative of the difficulties in terminology are 24 cases of basaloid adenocarcinoma reported by Chomette et al (1991) who regarded them as variants of adenoid cystic carcinoma. Gallimore et al (1994) in reporting three cases of what they termed 'basaloid carcinomas' also distinguished one of them which they regarded as a typical basal cell adenocarcinoma from the others which were high-grade tumours. Raslan et al (1995) have described the immunohistochemical and ultrastructural findings in a case and reviewed the literature.

The peak age incidence appears to be in the sixth decade and all patients have been adults. The parotid glands are the usual site.

**Microscopy**

Basal cell adenocarcinomas usually consist of multiple nodules of basaloid epithelial cells of two types. One type is small and dark with scanty cytoplasm. The other cells are larger, polygonal or more elongated, with eosinophilic or amphophilic cytoplasm and a pale basophilic nucleus, and frequently surrounded by the smaller cells. Palisading of the peripheral cells is less prominent than in basal cell adenomas, but the configurations of the benign and malignant types are similar (Figs 7.70 and 7.71). Like basal cell adenomas, solid, trabecular, tubular and membranous types may be recognized but frequently more than one pattern is present. In the tumour nodules, the larger cells may form small whorls in which there is sometimes squamous differentiation. Small lumens or tubules are occasionally present. Cellular and nuclear pleomorphism, foci of necrosis and moderate mitotic activity are sometimes seen, but are not conspicuous.

A distinctive feature is the frequent presence of sharply defined, hyalinized, periodic acid-Schiff-positive perinodular basal lamina which can also be enclosed as intercellular droplets. Also suggestive of the relationship of these basal cell adenocarcinomas to membranous basal cell adenomas is their association with dermal cylindromas of the scalp, as in two cases described by Ellis and Gnepp (1988).

Perineural, intravascular growth or invasion of surrounding tissues is frequently evident. Such infiltration may be seen in cytologically benign tumours of this type and is an
important feature distinguishing them from basal cell adenomas. Williams et al (1993) studied
the immunohistochemistry of 11 basal cell adenomas and 23 basal cell adenocarcinomas but
concluded that it was not possible to distinguish them by this means.

**Behaviour and prognosis**

Limited data are available. In the largest series so far reported (Ellis and Wiscovitch,
1990), follow-up of the 29 patients was incomplete. Of 25 patients on whom information was
available, seven had recurrences, metastases developed in three, but 10 remained alive and
well for 5-10 years after diagnosis. One of the infiltrative tumours recurred more than once
and finally metastasized after nearly 11 years. Gallimore et al (1994) noted that the well-
differentiated tumour they described, had been present for three years before treatment but
by then was causing severe pain and facial palsy and had extended into the nasopharynx and
skull base. The two less well-differentiated examples that they described grew rapidly. One
developed extensive metastases to lymph nodes and the other died within weeks, probably
from a cerebral metastasis.

**Treatment**

On the basis of their reported behaviour, these tumours are generally regarded as
relatively low-grade adenocarcinomas in most cases. They probably require at least total
conservative parotidectomy, though Ellis and Wiscovitch (1990) noted local recurrence in
28% of their cases and lymph-node involvement in 12%. Adjuvant radiotherapy may be
advisable.

If there is involvement of the facial nerve or lymph nodes or both, radical
parotidectomy and neck dissection is required.

**Sebaceous Carcinoma**

Although sebaceous differentiation is sometimes seen in the parotid glands and
occasionally seen in pleomorphic adenomas, sebaceous tumours of salivary glands are
uncommon. Out of 125 salivary sebaceous neoplasms reviewed by Gnepp (1983), 52 were
sebaceous adenomas or lymphadenomas, 19 were sebaceous carcinomas, only three were
sebaceous lymphadenocarcinomas while 51 were other tumours containing some sebaceous
differentiation. Most of these sebaceous neoplasms were in the parotid glands. The peak age
incidence was in the seventh decade.

Baillet et al (1992) showed that rare though they were, sebaceous carcinomas of
salivary glands were the most frequent extraocular sebaceous carcinomas in the head and neck
region. Of 91 of these tumours, 26 were in the parotid and one in the submandibular gland.
Eighteen per cent of the patients with salivary gland tumours died from their disease within
two to five years and only 46% were apparently tumour-free after a mean follow-up period
of four years.

Sebaceous lymphadenocarcinomas have more recently been categorized as 'sebaceous
carcinoma' with 'lymphoid stroma' as described below.
Sebaceous carcinomas give rise to painful masses, varying degrees of facial palsy and may become fixed to the overlying skin.

**Microscopy**

Sebaceous carcinomas consist of sebaceous cells showing variable degrees of cellular pleomorphism and nuclear atypia. The cells form sheets or nests (Figs 7.2 and 7.73). Despite apparent encapsulation, there is infiltration of surrounding tissues and perineural invasion may also occasionally be seen.

In isolated cases, oncocytes and foreign-body reactions to extravasated sebum, with histiocytes and giant cells, have been described. However, a dense lymphoid stroma with germinal follicles is, by definition, absent.

Although the typical features of sebaceous carcinomas have been described, the differentiation of low-grade examples from sebaceous adenomas may be difficult. In addition, some epidermoid carcinomas show foci of sebaceous differentiation. The presence of fat but absence of mucin may be useful in differentiating sebaceous tumours from mucoepidermoid carcinomas.

**Behaviour and prognosis**

Of 18 cases for which follow-up data were available, survival ranged from 8 months to 13 years, but five patients died from their disease within 5 years of diagnosis. The longest survival (13 years) was in a 22-year-old patient. The treatment of these cases ranged from local excision to parotidectomy with, in some cases, postoperative radiotherapy or chemotherapy.

**Treatment**

In view of the reported recurrences after limited resections, as radical a parotidectomy as possible, in keeping with the clinical presentation, is probably the treatment of choice.

**Sebaceous Carcinoma with Lymphoid Stroma (Sebaceous Lymphadenocarcinoma)**

The parotid glands are the most frequently affected but this tumour does not appear to have any distinctive clinical features. Unlike undifferentiated carcinoma with lymphoid stroma, its sebaceous counterpart has no special racial distribution.

**Microscopy**

The essential features are foci of sebaceous cells which show varying degrees of loss of differentiation, in a dense lymphoid stroma, sometimes with follicle formation. Intermingled with the malignant sebaceous cells are foci of apparently benign sebaceous tissue and there may be foreign-body reactions to extravasated sebum. This may be helpful in the differential diagnosis, though granulomatous reactions can also be seen in infarcted Warthin's tumours. There is partial encapsulation but local invasive activity.
Behaviour and prognosis

Limited information is available about these rare tumours. One patient had had the tumour for 20 years, while another had a solitary lung metastasis more than 13 years after treatment. Overall, these tumours appear to be of lower-grade malignancy than sebaceous adenocarcinomas without lymphoid stroma.

Treatment

In view of the potential of these tumours for metastasis, total conservative parotidectomy appears to be advisable but more radical surgery may be dictated by the preoperative behaviour of the tumour.

Oncocytic Carcinoma (Malignant Oncocytoma)

This must be the most uncommon of all primary salivary gland tumours.

Clinical features

The parotid gland is chiefly affected and only isolated cases have been reported in other glands. Most patients have been over 45 years and their mean age has been about 65 years. There seems to be no significant difference in sex distribution.

The usual manifestation has been an asymptomatic swelling but pain has been reported in a few cases.

Microscopy

Many of the earlier cases do not fulfil the two essential criteria of having oncocytes as the tumour cells and clear evidence of malignancy. Fifteen cases fulfilling these criteria, from the files of the AFIP, have been reviewed and nine further cases of oncocytic adenocarcinoma have been reported by Goode and Corio (1988) who have attempted to define its characteristics. All showed invasive activity or involvement of lymph nodes, and, in the majority of cases, gross pleomorphism. An initial diagnosis of oncocytic adenoma had been made in several cases. However, even Goode and Corio (1988), though they recognize malignant change in an oncocytic adenoma as a category, do not distinguish it from adenocarcinoma with extensive oncocytic change. They also believe that cytologically benign oncocytomas can occasionally metastasize as discussed in Chapter 6. One reason may be that, as Sugimoto et al (1993) have shown, a malignant variant and its metastases can show remarkably little cellular pleomorphism and very few mitotic figures.

The tumour cells resemble those of a benign oncocytoma in that they are rounded or polygonal and have distinctly eosinophilic, granular cytoplasm, but differ in that there is noticeable pleomorphism, both nuclear and cellular, and variable numbers of mitoses (Fig. 7.74). Also unlike benign oncocytoma, the cells may be in solid masses, cords, trabeculae or in papillae with small cysts, as well as in the expected alveolar arrangement. The oncocytic nature of these cells may be confirmed by staining with PTAH or BAAF to confirm mitochondrial proliferation, or may be established unequivocally by electron microscopy.
The malignant nature of such tumours, irrespective of their cytology, is confirmed by evidence of invasion of surrounding tissues, such features as perineural infiltration or by the appearance of metastases.

**Behaviour and prognosis**

Oncocytic carcinomas have a high incidence of recurrence after local excision and this has been followed by metastasis. Of the 30 cases reviewed by Ellis and Gnepp (1988), 12 had cervical lymph node and eight had distant metastases. Eight patients died from their tumours.

Unfavourable prognostic features, Goode and Corio (1988) suggest, are a large primary tumour and, microscopically, a predominantly cystic pattern or gross pleomorphism or both.

**Treatment**

Information is limited, but the behaviour of many of the reported cases of this rare tumour suggests that as radical a parotidectomy as is consistent with the preoperative clinical behaviour is probably the treatment of choice. Prophylactic neck dissection may have to be considered in view of the high reported incidence of nodal disease. Supplementary radiotherapy may also be considered though its value is uncertain.

**Adenocarcinoma Not Otherwise Specified**

The term 'adenocarcinoma (not otherwise specified)' is restricted to those carcinomas showing formation of duct-like structures without significant variation on this theme and lacking any features of a pleomorphic adenoma. These typical adenocarcinomas are described first; mucinous and papillary cystic adenocarcinomas are readily recognizable variants.

Other types of salivary carcinomas, which do not resemble typical adenocarcinomas which arise in such tissues as the gut, have been identified in increasing numbers as described in earlier sections. The inclusion of such subtypes into the general category of 'adenocarcinoma' in the past has made it difficult as yet to interpret earlier reports of behaviour.

Adenocarcinomas (all major types) formed 5% of 3500 epithelial salivary gland tumours, and 23% of carcinomas in our material. They comprised 3% of parotid but 5% of submandibular, 11% of sublingual and 13% of tumours of minor glands. However, the Göttingen and Hamburg registries record that they form between 10 and 12% of malignant salivary gland tumours.

**Clinical features**

The peak age incidence for adenocarcinomas is between the sixth and eighth decades; men appear to be more frequently affected than women in the ratio of almost 2:1. Rapid growth, pain, fixation to deep or superficial tissues and occasionally, ulceration through the skin are typical signs and symptoms in a significant number of patients. Seifert et al (1986) noted that 40% of adenocarcinomas caused facial palsy.
Microscopy

Even when carcinomas arising in pleomorphic adenomas or other tumours are excluded, several subtypes of salivary gland adenocarcinomas can be identified, as mentioned earlier, and inevitably also, variable degrees of differentiation are seen. Seifert et al (1986) recognized tubular, papillary and rare solid variant. A more recent tendency is to categorize members of this diverse group as separate entities as indicated in the classification (see Table 6.2, p. 82).

Tubular type

This, the most readily recognized form of adenocarcinoma, is characterized by production of ducts formed by cells showing variable degrees of atypia (Fig. 7.75). The quality of differentiation of the ducts may sometimes be unrelated to the degree of atypia of the surrounding cells; well-formed ducts may be produced by cells showing gross atypia and vice versa.

Papillary cyst adenocarcinoma

This has a predilection for the palate and is rare in the major glands. The typical appearances are folds of epithelium projecting, as papillary or frond-like ingrowths, into irregular cystic spaces. This epithelium may be multilayered and have columnar or goblet-shaped mucous cells on its surface. Small foci of solid epithelium, some of the cells of which may have clear cytoplasm, may also be seen.

The epithelium may, as with comparable thyroid carcinomas, lack any cytological features of malignancy, with the result that it appears to be benign (Fig. 7.76). In addition, some areas of polymorphous low-grade adenocarcinomas show a conspicuous papillary cystic pattern and may in the past have been categorized as papillary cystic adenomas (Fig. 7.77).

Mills et al (1984) reported five cases from the palate and their microscopic features, and also reviewed seven earlier cases. The misleadingly bland appearance of the cells of many papillary cystadenocarcinomas is emphasized by the fact that three of these five cases were initially interpreted as benign. One of them, which had shelled out freely at operation, caused the death of the patient 33 years after the original diagnosis, despite extensive surgery and radiotherapy. In another such case seen by us, a patient who had a tumour categorized as a papillary cystic adenoma of the palate, which was widely excised, remained asymptomatic for 15 years but then died with widespread metastases. It is doubtful therefore whether it is justifiable to accept the existence of a papillary cystic adenoma of the palate, which was widely excised, remained asymptomatic for 15 years but then died with widespread metastases. It is doubtful therefore whether it is justifiable to accept the existence of a papillary cystic adenoma of the palate, except in the terms described in Chapter 6, and it is probably wise to regard all papillary cystic salivary gland tumours as carcinomas, though of very low-grade in some cases. In one of the patients reported by Mills et al (1984), metastases appeared in the regional lymph nodes 21 years after presentation. Of the seven earlier cases reviewed by them, only three patients were alive and without evidence of tumour, approximately 42 months after treatment. Of the five more recent patients, two had had recurrences seven and eight years respectively, after initial treatment. Mostofi et al (1993) found 22 reports of low-grade papillary cystic adenocarcinomas of minor salivary glands and confirmed that 27% of them recurred between 1 and 19 years after treatment. However, the period of follow-up of seven of those without recurrences was only three years or less.
High-grade papillary cystadenocarcinomas may also be seen but should not be difficult to recognize.

**Mucinous adenocarcinoma**

Mucin secretion may be prominent in adenocarcinomas, as described by Blanck et al (1971), and an uncommon variant is the mucin-secreting adenocarcinoma resembling its counterpart from the breast. Microcysts may also form (Figs 7.78 and 7.9). In the differential diagnosis, mucoepidermoid carcinomas may have to be distinguished.

**Behaviour and prognosis**

Typical adenocarcinomas usually grow rapidly, are aggressively invasive, and spread to regional lymph nodes and more distant sites. As with most other carcinomas, the prognosis depends on the rapidity of development of the tumour and its extent at operation. Poorly differentiated tumours have frequently involved lymph nodes when first seen and have a correspondingly poor prognosis. By contrast, well-differentiated papillary cystadenocarcinomas may behave in a benign fashion for many years as described earlier. Probably for this reason, adenocarcinomas of minor salivary glands appear to have a better prognosis than those arising in the parotid glands according to Seifert et al (1986).

It is not possible to give accurate five- and ten-year survival rates as most series have been small and there is sometimes doubt as to how widely the term 'adenocarcinoma' has been interpreted. The figure of a five-year survival rate of 40%, given by Seifert et al (1986), is probably as good a guide as any.

**Treatment**

Radical parotidectomy or en bloc resection of other glands is probably unavoidable in most cases; neck dissection may also be necessary. These tumours are not highly radiosensitive; nevertheless, postoperative radiotherapy is frequently given. Even this may not be curative, but in the case of low-grade papillary-cystic adenocarcinomas, many years of normal life are possible before recurrences appear.

**Sclerosing Adenocarcinoma**

This exceedingly rare type of tumour which does not seem to have been described elsewhere, appears to be a counterpart of sclerosing carcinomas of the breast. It induces fibrosis of the gland but tumour cells surround duct-like or microcystic spaces (Fig. 7.80). The tumour cells tend to be compressed by the fibrous stroma so that their carcinomatous nature may be difficult to discern and the appearances may mimic inflammatory sclerosis or a Küttner tumour. Careful examination is therefore required to recognize the malignant nature of this lesion (Fig. 7.81).
Epidermoid (Squamous-Cell) Carcinoma

Squamous metaplasia is a common feature of pleomorphic adenomas, but primary epidermoid carcinomas of salivary glands are rare. In some series, the incidence may have been inflated by the inclusion of microscopically similar tumours such as poorly differentiated mucoepidermoid carcinomas, squamous-cell carcinomas originating in the skin or oral mucosa, and metastatic tumours.

In the series of Seifert et al. (1986), squamous-cell carcinomas accounted for 10% of all salivary gland carcinomas or 2.0% of all epithelial tumours. In our material, it formed only 5% of salivary gland carcinomas or 1% of epithelial tumours. The most common site is the parotid gland, though this tumour is relatively more frequent in the minor and submandibular glands; in our material, none was found in the sublingual glands.

Clinical features

The elderly are predominantly affected and in our material, the mean age was 71 years and the range 50-90 years. Males predominated over females in the ratio of 2.4:1.

In most cases, the history is relatively short and the tumour is often hard and fixed. The regional lymph nodes are involved early and facial palsy is common.

Microscopy

The appearances range from well-differentiated tumours, consisting of sheets of squamous cells with clearly visible intercellular bridges and abundant keratinization (Fig. 7.82), to poorly differentiated examples with smaller cells having relatively little cytoplasm and without keratin formation. Active invasion and destruction of surrounding tissues is evident. The stroma is fibrovascular and contains a predominantly lymphocytic infiltrate. In short, the appearances are those of squamous-cell carcinomas in general.

Mucin production is not seen and if detected by appropriate stains, the tumour is probably a poorly differentiated mucoepidermoid carcinoma. However, squamous-cell carcinomas are reported by Takeuchi et al. (1981) to have a high glycosaminoglycan content.

In parotid gland material, it may be impossible to decide whether or not a squamous-cell carcinoma is a primary tumour.

Behaviour and prognosis

Squamous-cell carcinomas tend to invade and spread rapidly, and involve regional lymph nodes at a relatively early stage. The five-year survival rate is probably about 40% but no large series of these uncommon tumours exists to establish either the prognosis or optimal mode of treatment with certainty.
Treatment

Radical parotidectomy (or en bloc resection of other salivary glands) and, if necessary, neck dissection, followed by postoperative radiotherapy, is the most appropriate form of treatment. A major factor which may limit the extent of the excision is the patient's age.

Squamous Carcinoma of Stenson's Duct

Carcinoma of Stenson's duct is even more rare than squamous-cell carcinomas of the parotid gland parenchyma and Haar et al (1991) could find fewer than 20 reports in the English literature.

Those affected range between 40 and 80 years and the usual presentation is a localized tender swelling. This may dilate the duct, produce a filling defect radiographically and thus simulate an inflammatory lesion. The diagnosis may therefore be delayed attempts to deal with the lesion by antimicrobial treatment. The patient's prognosis is likely to be adversely affected, as happened in the case shown here.

Microscopy

These tumours range from well to poorly differentiated, but otherwise typical squamous-cell carcinomas, and the origin from the lining epithelium of Stenson's duct should be discernible. The duct may fill with keratin (Fig. 7.3). At the time of diagnosis, this may be obscured by the spread of the tumour, but its precise site of origin probably does not significantly affect either the management or prognosis.

Carcinoma of Stenson's duct must be distinguished from a carcinoma arising from a nearby minor buccal gland.

Management

Treatment is by radical excision and radiotherapy. Because of its superficial origin, symptoms and diagnosis should be earlier than in the case of intraglandular squamous-cell carcinomas unless the picture has been complicated by inflammation. However, so few cases have been reported and the follow-up periods have been so short that it is not possible to gain any useful idea of the prognosis.

Other primary carcinomas of Stenson's duct

The majority of reported carcinomas of Stenson's duct have been squamous as described earlier, but of twelve carcinomas of Stenson's duct reviewed by Haar et al (1991), five were mucoepidermoid carcinomas.

Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare neoplasm which, as the name implies, shows both adenoid and squamous differentiation. There have been reports of such tumours in many sites in the body and Gerughty et al (1968) described ten cases, of which five were in the nasal
or laryngeal areas and five in the mouth. Ellis and Gnepp (1988) have found that this tumour, when in salivary glands, only affects minor oral glands. They reviewed 40 cases from the Armed Forces Institute of Pathology (AFIP) files.

The main sites affected appear to be the floor of the mouth, posterior tongue and faucial area. Male patients have outnumbered females in the ratio of 2:1 and the peak age incidence has been in the sixth and seventh decades. Clinically, the tumour appears similar to a squamous-cell carcinoma of the mouth.

**Microscopy**

Distinction should be made between adenosquamous carcinoma and pseudoglandular areas in a squamous-cell carcinoma. This latter appearance, which according to Ellis and Gnepp (1988) is seen only in carcinomas of the oral aspect of the lower lip, results from malignant acantholysis of the epidermoid cells to produce pseudolumens (Fig. 7.84).

Adenosquamous carcinoma has distinct and separate areas of adenocarcinoma and of epidermoid carcinoma and thus differs from mucoepidermoid carcinoma, in which glandular and epidermoid differentiation are contiguous. Ellis and Gnepp (1988) consider that squamous carcinoma or carcinoma *in situ* of the overlying epithelium, with underlying adenocarcinomatous change, is an important criterion of diagnosis (Figs 7.85 and 7.86). The adenocarcinoma is typically of ductal type and can be seen intermingling with the squamous carcinoma, but separate areas of both types of carcinoma are also seen.

Gerughty *et al* (1968) speculated that adenosquamous carcinoma might originate from excretory duct epithelium with spread to the oral mucosa. The reserve cells of the excretory duct epithelium, it is suggested, have the potential for both ductal and epidermoid differentiation. However, the association between a superficial squamous-cell carcinoma with a deeper adenocarcinoma could also be interpreted as the intermingling of two separate primary tumours.

**Behaviour and prognosis**

The limited information from the few reported cases suggest that adenosquamous carcinoma is aggressive. All five cases reported by Gerughty *et al* (1968) spread to the regional lymph nodes, even though they were only 1 cm in size when biopsied. Three of the five also metastasized to the liver and lung.

**Treatment**

Radical parotidectomy or *en bloc* resection of other glands appears to be necessary. Radiotherapy and prophylactic neck dissection should be considered but their effect on survival is unknown.
Undifferentiated and Neuroendocrine Carcinomas

The term 'undifferentiated carcinoma', as defined by the World Health Organization, is applied to carcinomas which do not show any microscopic features which allow them to be included in any of the categories already described. These tumours should also be distinguished from another entity, namely, 'undifferentiated carcinoma with lymphoid stroma' which is described later.

Undifferentiated tumours comprised 5% of malignant salivary gland tumours in the Hamburg registry (Seifert et al, 1986) and 8% in the BSGTP material. This represents between 1.4% (Seifert et al, 1986) and 1.9% (BSGTP) of all epithelial tumours. They were most frequently found in the parotid glands (63% of all the undifferentiated carcinomas in our material), formed a modest proportion (11%) of sublingual gland tumours and submandibular gland tumours (4%) but were rare in other glands.

In contrast with these figures, Hui et al (1990) have noted that in some reports, undifferentiated carcinomas had been considered to form ≤ 30% of malignant salivary gland tumours. Of 32 tumours which had been so designated previously, these workers had to exclude 16 because they failed to fulfil the necessary criteria when a variety of stains and immunohistochemistry were used. Exclusions fell into the following categories: (1) non-epithelial tumours; (2) metastatic tumours such as oat-cell carcinoma of the lung; and (3) 'lymphoepithelial carcinoma' (undifferentiated carcinoma with lymphoid stroma). They also noted that some tumours had been designated undifferentiated on insufficient material or were found on further examination to be better differentiated than was earlier thought. In assessing previous reports, therefore, these considerations should be borne in mind.

Gnepp and Wick (1990) found that approximately 41 of these tumours had been reported. Nagao et al (1982) in reporting 18 undifferentiated carcinomas of the parotid glands, found that 12 were small-cell in type and the remainder, large-cell. Hui et al (1990) in their re-examination of 16 undifferentiated carcinomas of salivary glands reported that 12 of them were small-cell (≤ 30 microm in diameter) and four were large-cell types.

Small-cell carcinomas, according to Gnepp and Ellis (1988) account for between 0.3 and 3% of salivary gland tumours and this variation in reported incidence presumably also results from variations in the criteria of categorization used in different centres. Gnepp et al (1986) suggest that true anaplastic small-cell carcinomas form only about 1% of undifferentiated carcinomas.

Clinical features

Gnepp and Wick (1990), in reviewing and re-examining previously reported cases, showed that of 11 patients with small-cell carcinomas, all except one were adults over 30 years, seven were over 65 years and there was little difference in the sex incidence. The mean age of the 16 patients reviewed by Hui et al (1990) was 67 years but there was a male predominance of 3:1. In the latter's series, patients complained of a non-tender mass that had been enlarging over a period of 1-7 months. The parotid glands are predominantly affected. Facial palsy is particularly common with this type of tumour and was present in 60% of the
patients of Seifert et al (1986). As might be expected of poorly differentiated tumours also, growth is rapid and the incidence of lymph-node metastases on presentation is high.

Microscopy

The nature of the cell of origin is not obvious by light microscopy and the usual picture is of almost non-descript sheets of cells. These cells may be predominantly round, large or small or spindle-shaped. The small-cells are almost featureless, uniform in size with round or oval nuclei and dense chromatin, inconspicuous nucleoli and scanty cytoplasm; mitoses may be frequent (Fig. 7.87). Large-cell undifferentiated carcinomas typically consist of round cells or three times larger than those of the small-cell variant and have vesiculated nuclei with several nucleoli.

The small-cell tumours may resemble lymphomas. However, immunohistochemistry should enable the necessary distinction to be made.

The tumour cells form sheets, irregular clusters, organoid nests or combinations of these features and there may be areas of necrosis. Small-cell carcinomas of salivary glands resemble oat- or intermediate-cell carcinomas of the lung but may show rudimentary duct formation. Crush artifacts may be seen.

A lymphocytic infiltrate of variable density is frequently present in a scanty fibrovascular stroma. Invasion and destruction of normal structures is usually obvious. Hui et al (1990) found that the most important feature suggesting a poor prognosis was neural invasion.

Small-cell neuroendocrine tumours

Like oat-cell carcinomas of the lung, neuroendocrine cells have been identified mainly in small-cell carcinomas of salivary glands (Fig. 7.88). However, the latter, like many other neuroendocrine cell tumours (Sobol et al, 1989) do not appear to produce active hormones, though occasional cases of salivary gland carcinomas associated with endocrine disturbances have been reported as discussed later.

Neuroendocrine cells in these tumours have been identified by their argyrophil properties (Grimelius staining) or chromogranin A staining, immunoreactivity and electron microscopy in the various reports (Fig. 7.89).

Chromogranin A positivity is regarded as a reliable marker of neuroendocrine cells since it is not produced by non-endocrine cells. However, the reliability of chromogranin for identifying neuroendocrine cells does not appear to have been confirmed by Gnepp and Wick (1990) who studied 11 small-cell carcinomas of major salivary glands. These tumours had previously been examined by electron microscopy and neuroendocrine granules had been found in eight. Immunostaining, using the avidin-biotin-peroxidase technique, was carried out for a variety of antigens. Keratin was the only antigen detected in all the tumours and epithelial membrane antigen was found in eight. Vimentin staining was positive in only two and neither of these had neuroendocrine granules. However, all the tumours were positive to some of the stains, and all except vimentin corresponded with the presence of neuroendocrine
granules to a variable degree. All the neuroendocrine granule-containing cells stained positively for NSE, Leu-7 and keratins but only one of them was chromogranin-positive. All but a few of the tumours lacking neuroendocrine cells also stained positively for keratins, Leu-7 and NSE. On the basis of these findings therefore, Gnepp and Wick (1990) concluded that even when electron-dense core granules could not be detected, all small-cell carcinomas of major salivary glands had some neuroendocrine characteristics.

Hui et al (1990) in their 16 undifferentiated carcinomas found ultrastructural evidence of neuroendocrine differentiation in five of the small-cell and in one of the large-cell carcinomas; four other small-cell carcinomas had no distinguishing ultrastructural features. Like Gnepp et al (1986), they found that none of the small-cell tumours that showed ductal differentiation contained neurosecretory granules.

Histogenesis

The origin of neuroendocrine cells in salivary gland tumours is speculative, but the most obvious assumption is that they are derived from the neural crest and are part of the neuroendocrine (APUD) tissue that is widely distributed in the body, particularly in the gastrointestinal tract, where it can give rise to the carcinoid syndrome. Disseminated neuroendocrine cells have also been found in normal parotid tissue but only on rare occasions. Nevertheless, there is little evidence for the presence of neural crest (Kulschitzky) cells in normal salivary tissue. More probably, therefore, undifferentiated duct cells become capable of neuroendocrine granule production in a comparable fashion to small-cell carcinomas of the lung and can develop electron microscopic features in common with the latter. This ectopic hormone production may be the result of abnormalities of expression of regulating genes rather than an origin in neuroendocrine cells.

Differential diagnosis

Some of the difficulties have been discussed earlier. Basal cell adenocarcinomas or solid (basaloid) adenoid cystic carcinomas may also be confused with undifferentiated carcinomas, but it is particularly important to distinguish them, as basal cell adenocarcinomas appear to be of considerably lower-grade malignancy.

The possibility of the salivary gland tumour being a metastasis from an asymptomatic primary in the lung or elsewhere, must also be considered as the prognosis is then likely to be hopeless. Bronchogenic carcinomas are one of the most frequent sources of metastases to many sites and in approximately 4% of them symptoms are first caused by secondary deposits. A case of bilateral parotid metastases from an oat-cell carcinoma of the lung has been reported by Cantera and Hernandez (1989), but metastases of bronchogenic carcinomas to salivary glands appear to be rare though they may form deposits in juxta-glandular nodes.

Behaviour and prognosis

Undifferentiated carcinomas are actively invasive and metastasize early. Although Gnepp et al (1986) estimated that the two- and five-year survival rates for neuroendocrine tumours were 70% and 46%, respectively, in the later series reported by Gnepp and Wick (1990), all but three of the nine patients in whom the outcome was known, had died within
periods of 1-51 months. The three remaining were alive and well after at least six years. Similarly Hui et al (1990) found that > 50% of their patients had recurrences after 2-26 months and a similar proportion had regional or distant metastases. Over 60% of these patients died from their disease within 2-54 months and only 25% were living without evidence of tumour for periods of ≤ 2 cm in diameter were alive after five years.

It is not possible to compare these survival rates with those of histologically similar carcinomas of the lung as most of the latter are too extensive for excision at the time of treatment and are treated by chemotherapy. Nevertheless, a 35% five-year survival rate has been reported after excision of operable, oat-cell lung tumours.

It does not seem that the presence of neuroendocrine features in undifferentiated salivary gland tumours confers any prognostic advantage and like chromogranin-positive tumours of some other sites such as the uterine cervix, colon or bladder may be particularly aggressive.

**Treatment**

The available data suggest that undifferentiated carcinomas should be widely excised and neck dissection carried out for clinically involved nodes. Postoperative radiotherapy is advisable. Metastasis when it takes place appears to be mainly via the bloodstream.

In the series reported by Hui et al (1990), all 16 patients had excision and 10 patients had ipsilateral neck dissections. All patients had postoperative radiotherapy and 10 patients had chemotherapy for recurrences or distant metastases. Nevertheless, as already described, the survival rates were poor.

**Other types of neuroendocrine salivary gland tumours**

Sugawara and Hagen (1988) reported ectopic adrenocorticotropic hormone (ACTH) production and Cushing's syndrome, associated with a tumour that they categorized as an adenoid cystic carcinoma in which high levels of immunoreactive ACTH were found. The patient had widespread metastases and died before the effect of removal of the salivary gland tumour could be assessed, but at autopsy the pituitary gland appeared normal. Earlier reports of ectopic ACTH production by salivary gland tumours include those of Cox et al (1970) and Marks et al (1975).

Also in contrast to small-cell endocrine tumours, Eusebi et al (1982), reported a neuroendocrine parotid gland carcinoma, which resembled a clear-cell tumour, had an organoid pattern and was associated with a carcinoid of the lung. Structurally, therefore, this tumour had resemblances to a jugulotympanic paraganglionoma which can occasionally involve the parotid region.

Hayashi et al (1987) have also reported undifferentiated carcinomas of salivary glands which contained neurosecretory granules but also squamous and clear cells. Earlier, Hayashi et al (1987) had reported immunoreactive vasoactive intestinal polypeptide (VIP) and positive Grimelius staining in an acinic cell carcinoma of the parotid but not in any samples of other
common types of salivary gland tumours.

**Carcinoma in Pleomorphic Adenoma (Ca Ex-Pleomorphic Adenoma) and Variants**

The term 'dysplasia in pleomorphic adenoma (intracapsular carcinoma)', as described earlier, is given to carcinoma cells within the boundaries of a pleomorphic adenoma but lacking evidence of invasion of surrounding tissues (Fig. 7.90). This change has also been termed 'in situ carcinoma'. If invasion can be confidently excluded, the tumour can be treated in the same way as a pleomorphic adenoma, but follow-up must be rigorous.

Malignant change in benign tumours in the body as a whole, is relatively rare. Over the years therefore, opinions have ranged from those that held that some pleomorphic adenomas were malignant from the start but that foci of carcinoma had been missed in the initial specimen, to the current view that carcinomas can genuinely arise in pleomorphic adenomas.

Convincing evidence of true carcinomatous change in a pleomorphic adenoma is the microscopic finding of both types of neoplasm in the same tumour. Further, the finding of foci of cellular atypia, mitotic activity and other signs suggestive of malignancy well within a pleomorphic adenoma (as described in the previous chapter) also suggests that an adenoma can undergo carcinomatous change.

**Clinical features**

The development of carcinoma in pleomorphic adenoma is suggested when localized tumours of many years standing show a sudden acceleration of growth or any other signs or symptoms typical of malignancy. It is clear that carcinoma develops mainly in long-standing pleomorphic adenomas; whereas the mean age incidence of the latter is 46 years, that of carcinoma in pleomorphic adenoma is almost two decades later. The frequency of carcinoma in pleomorphic adenoma also rises with its duration of existence (Eneroth et al, 1968) and the risk increases from about 1.5% after five years to nearly 10% after fifteen years. In the material analyzed by Seifert et al (1986), 87% of carcinomas in pleomorphic adenoma developed after one or more recurrences and had an average latent interval of 16 years. In the remaining 13%, the duration of existence of the untreated pleomorphic adenomas was seven years.

The frequency of malignant change in recurrent pleomorphic adenomas underscores the necessity to eradicate pleomorphic adenomas at the first operation as discussed in Chapters 6 and 9.

Carcinoma in pleomorphic adenoma is one of the most common types of carcinoma of salivary glands. In our material, it accounted for 5% of all epithelial tumours and 20% of carcinomas of salivary glands. A similar figure is reported by Seifert et al (1986). In the parotid and sublingual glands, it was the most common type of carcinoma, but in the submandibular and minor salivary glands, adenoid cystic carcinoma was more frequently encountered. Overall, however, 80% of these tumours arose in the parotid glands.
As mentioned earlier, the mean age of those affected is 63 years with a peak incidence also in the seventh decade. There appears to be little difference in sex distribution. The typical history is that of a long-standing and slowly growing tumour, the growth rate of which has suddenly accelerated or which has started to become painful or shown other clinical signs suggestive of malignancy.

**Microscopy**

The salient features are the juxtaposition of typical pleomorphic adenoma and a carcinoma (Fig. 7.91). The latter is usually an adenocarcinoma or poorly differentiated, and in most cases there is an abrupt transition from the adenoma. Mucoepidermoid, adenoid cystic or squamous-cell carcinomas are less common. More than one type of carcinoma can arise in a pleomorphic adenoma (Thackray and Lucas, 1974), but this is rare.

Some pleomorphic adenomas become increasingly hyalinized over the course of years and it is often in one of these scarred nodules that carcinomas develop (Figs 7.92 and 7.93). As a consequence, such nodules should be closely examined for signs of malignancy (Fig. 7.94).

Carcinoma developing in a multinodular recurrence of a pleomorphic adenoma may be evident in only one of the nodules so that both the benign and malignant parts of the tumour can be seen side by side (Fig. 7.95).

It must be emphasized that, in making this diagnosis, the microscopic features of malignancy should be unequivocal with clear signs of destruction of normal tissues or invasion and not merely those of intracapsular atypia as mentioned earlier.

Confident recognition of the primary adenoma is sometimes difficult. Little of it may remain or what remains may have degenerated. Remnants of the myxochondroid stroma and cartilage, in particular, appear to be most persistent components. The diagnosis of carcinoma in pleomorphic adenoma is unlikely to come to mind if the adenomatous element is not obvious but it is important to recognize this possibility because of its effect on the prognosis.

**Behaviour and prognosis**

Once malignant change has developed, the behaviour is that of the carcinomatous component. However, it appears that the prognosis of carcinoma in pleomorphic adenoma is poorer than that of comparable carcinomas developing de novo. Seifert et al (1986) quote a five-year survival rate of only 25% while Thackray and Lucas (1974) suggest that the majority of patients die within three years.

**Treatment**

Radical parotidectomy with sacrifice of the facial nerve and neck dissection, if necessary, is required.
Myoepithelial Carcinoma (Malignant Myoepithelioma)

As described in Chapter 6, spindle-shaped myoepithelial cells can occasionally predominate in pleomorphic adenomas and, rarely, a pure spindle cell myoepithelioma may be seen. Malignant change involving these myoepithelial cells is rare. Cases have been reported by Crissman (1971), Dardick (1985), Singh and Cawson (1988), and Di Palma and Guzzo (1991) who also reviewed previous reports. Despite its distinctive appearances, myoepithelial carcinoma must be regarded as a variant of carcinoma in pleomorphic adenoma.

In the case reported by Singh and Cawson (1988), the malignant myoepithelial component had developed in, and overgrown, a pleomorphic adenoma to form a giant tumour (775 g) which extended down to the clavicle and had been present for fifteen years. There was no pain or facial palsy.

Microscopy

The most obvious feature is the pseudosarcomatous proliferation of the myoepithelial cells which are predominantly spindle-shaped, with pleomorphic hyperchromatic nuclei. Abnormal mitoses may be present (Figs 7.96 and 7.97). The cell cytoplasm is fibrillar or vacuolated and there is strongly positive staining for actin, vimentin and S-100 protein. Interspersed among the spindle cells may be multinucleate giant cells and occasional plasmacytoid cells. Any contiguous pleomorphic adenoma (Fig. 7.98) shows the expected variety of appearances including myxochondroid differentiation and calcification, but transition of some of the cells to pleomorphic, malignant spindle-shaped myoepithelial cells may also be seen. Previously reported cases such as those reported by Crissman et al (1977) and Dardick (1985) showed generally similar features but the latter also described the ultrastructural changes. This patient had no evidence of recurrence or metastases after three years.

Benign plasmacytoid myoepitheliomas have been said to have no potential for malignant change. However, Di Palma and Guzzo (1993) reported two among eight malignant myoepitheliomas. These showed moderate to marked atypia and infiltrative growth.

Treatment

Too few cases have been reported to be certain that the prognosis of myoepithelial carcinoma is any more favourable than that of the more common type of carcinoma in pleomorphic adenoma. Radical parotidectomy with neck dissection, if necessary, seems therefore to be the most appropriate form of treatment.

Carcinosarcoma

Though a potential for sarcomatous change in the mesenchymal products of the myoepithelial cells might be expected and sarcomas of salivary glands are occasionally found, malignant change in both types of cellular components of pleomorphic adenomas is exceptionally rare. Batsakis (1982) mentions four examples that he had seen and there have been a few scattered reports, such as three examples among 40 cases of malignant mixed tumours found by Tortoledo et al (1984). More recently, Ellis and Gnepp (1988) identified
five cases from the AFIP files and Toynton et al (1994), have added another which arose in the lip of a 32-year-old male.

**Clinical features**

Limited information is available from the few reported cases. Those from the AFIP files were in patients from 58 to 66 years old, apart from one of 29 years. In a remarkable case reported by Jacobson et al (1973), the patient was an 8-year-old girl with a pleomorphic adenoma of the parotid gland. It recurred repeatedly over a period of 39 years and finally metastasized to the regional lymph nodes and humerus. Though not reported as such, the metastasis appears from the illustration to be sarcomatous. In our material, a carcinosarcoma in the palate of a female aged 60 years, caused pain and ulceration. Despite radical surgery, the patient developed bilateral cervical nodes within a period of weeks and died shortly afterwards. The relief of pain from the palatal lesion was soon replaced by excruciating pain from the neck, and required large doses of opioids for its control.

**Microscopy**

The epithelial component consists of moderately well to poorly differentiated carcinoma in most cases (Fig. 7.99), but papillary cystadenocarcinoma and epithelial-myoeptihelial carcinoma have also been described by Ellis and Gnepp (1988).

The sarcomatous component has usually been chondrosarcoma (Fig. 7.100) or osteosarcoma, as might be expected from the chondroid differentiation commonly seen in the stroma of pleomorphic adenomas. In a case reported by Talmi et al (1990), a fibrosarcoma was associated with ductal carcinoma in a parotid tumour. In the case reported by Toynton et al (1994), the carcinoma was largely undifferentiated but with some acinar differentiation while the mesenchymal component was a fibrosarcoma.

Differentiation from pseudosarcomatous change in a myoepithelioma can be made by immunohistochemistry.

**Behaviour and prognosis**

Little information is available but it seems likely that the sarcomatous component would worsen the prognosis. This seems to be borne out by the patients reported by Tortoledo et al (1984) all of whom died from their disease, as did our patient. However, the patient reported by Talmi et al (1990), whose tumour was only 1.5 cm in diameter, remained well 11 months after operation.

**Treatment**

Information about these rare tumours is little better than anecdotal, but radical surgery seems to be indicated for early cases and may at least provide some palliation of pain, but, in advanced cases, the decision as to whether any surgery is likely to be of long-term or even of short-term benefit may be exceedingly difficult.
Metastasizing Pleomorphic Adenoma

Foote and Frazell (1954) described cytologically benign pleomorphic adenomas which were invasive and could metastasize. Moreover, the secondary deposits retained the benign cytological features of the primary growth. This type of carcinoma is sometimes termed 'malignant mixed tumour' to distinguish it from carcinoma in pleomorphic adenoma. However, this term is sometimes also interpreted to mean both sarcomatous and carcinomatous change in a tumour. The present terminology is by no means entirely satisfactory but despite the variety of meanings applied to the term 'malignant mixed tumour', it seems to be widely favoured.

Metastasizing pleomorphic adenoma illustrates the difficulty, by no means unique to salivary gland tumours, of predicting malignant behaviour from cytological appearances alone. This problem is one where, like carcinoma in pleomorphic adenoma, aspiration cytology might be misleading.

Since Foote and Frazell (1954) drew attention to these tumours, there have been few other reports and little clinical data have accumulated. However, it is clear that they are considerably more uncommon than carcinoma in pleomorphic adenoma. Chen (1978) reported one case and reviewed seven others, while, from the many specimens in the AFIP files, Ellis and Gnepp (1988) found only two cases that had metastasized.

From among the 151 carcinomas in pleomorphic adenoma and 1918 pleomorphic adenomas in our material, only two metastasizing pleomorphic adenomas were found.

Clinical features

The limited data available suggest that the age range is wide and that the parotid gland has been the site in most cases. Qureshi et al (1994) reported a case in which a bone metastasis showed identical histopathology to a parotid gland pleomorphic adenoma treated 16 years earlier. There had been no local recurrence. In reviewing the literature they found 23 acceptable cases. Males and females were equally frequently affected. Patients' ages ranged from 12 to 73 years (mean age 35 years) and intervals between primary treatment and appearance of metastases ranged from 2 to 52 years (mean interval 19.8 years).

Microscopy

The diagnostic criteria are cytological features consistent with those of a pleomorphic adenoma, but with the difference that there are clear signs of local tissue invasion and destruction (Figs 7.101 and 7.102) or of metastasis. Absolute confirmation of the diagnosis is the development of metastases which reproduce the benign cytological characteristics of the primary. Lack of encapsulation, mild atypia or occasional mitoses are not sufficient for diagnostic purposes as these changes can be seen in pleomorphic adenomas. Greater degrees of cellular atypia, comparable to that in carcinomas but localized within the substance of a pleomorphic adenoma, as mentioned earlier, may precede development of carcinoma in pleomorphic adenoma, but are not, therefore, a feature of metastasizing pleomorphic adenoma which, by definition, is cytologically benign. Wenig et al (1992) found neither histological variables nor flow cytometry to be successful for predicting metastasis.
**Behaviour and prognosis**

Little information is available on the prognosis of these tumours. Their behaviour is that of carcinomas, but even though the cytology suggests that they are of low grade, this is of little help in view of their ability to metastasize and, rarely, to cause the death of patients.

**Treatment**

In view of the ability of these tumours to metastasize, wide surgical excision and neck dissection, if necessary, appears to be the treatment of choice.

**Carcinoma in Warthin's Tumour**

Malignant change in the epithelial component of Warthin's tumours has been reported on exceedingly rare occasions. These reports were reviewed by Seifert et al (1986) who quote cases of squamous-cell, adenocarcinoma and undifferentiated carcinomas developing in Warthin's tumours and show examples. Since then, Onder et al (1990) have reported a case of poorly differentiated adenocarcinoma in Warthin's tumour with severe dysplasia of the oncocytic cells in other areas. They have also summarized the features of 14 previous reports in the English-language literature. These show that the carcinomas can be adenocarcinomas, squamous cell or undifferentiated. Bengoechea et al (1989) have reported an unusual case of an oncocytic carcinoma in a Warthin's tumour with visible transition between the benign and malignant oncocyes.

To make the diagnosis of carcinoma in Warthin's tumour, it is necessary to find convincing evidence of the typical columnar epithelium undergoing dysplastic change and to exclude another, synchronous tumour. It is also necessary to exclude metastases into a Warthin's tumour and to distinguish the tumour from undifferentiated carcinoma with lymphoid stroma ('lymphoepithelial carcinoma').

**Treatment**

Virtually all the reported cases have metastasized and radical treatment therefore seems appropriate.

Lymphomatous change in Warthin's tumour is discussed in Chapter 8.

**Undifferentiated Carcinoma With Lymphoid Stroma**

The terminology is confusing. The tumour has also been termed malignant lymphoepithelial tumour and lymphoepithelial carcinoma. So-called 'benign lymphoepithelial lesion' is a lymphoproliferative disorder and not generally believed to be a neoplasm. The same histological appearances are characteristic of Sjögren's syndrome as discussed in Chapter 4. There is also a high risk of lymphoma in benign lymphoepithelial lesion, as discussed in Chapter 8. The term 'malignant lymphoepithelial lesion' is therefore misleading in that it suggests a relationship with benign lymphoepithelial lesion. Currently, therefore, to distinguish this tumour from lymphoma in a benign lymphoepithelial lesion, the clumsy term 'undifferentiated carcinoma with lymphoid stroma' is used for this tumour with an unusual
racial distribution and rarely associated with Sjögren's syndrome.

**Clinical features**

Undifferentiated carcinoma with lymphoid stroma is found in Arctic Eskimos, and accounts for the unusually high incidence of salivary gland cancer in these races. It is also found in Chinese, particularly from southern China. Saw et al. (1986b) reported eight cases, seven of which were in southern Chinese and one in an Anglo-Chinese. A relationship with the Epstein-Barr virus has been suggested. In non-mongoloid patients, this tumour is rare, but two cases were reported in Britons (James and Ellis, 1986). Ellis and Gnepp (1988) reviewed cases from reports and found 73 cases in the AFIP files. Of these, 20 (27.4%) were in non-mongoloids. However, in view of the type of population represented in this material, it seems possible that these unusual (non-mongoloid) cases have been overrepresented.

Krishnamurty et al. (1987) in a detailed review of this tumour in Alaskan Eskimos and American Indians, calculated that incidence rates per 100,000 of salivary gland cancer (of which undifferentiated carcinoma with lymphoid stroma accounts for approximately 75% of cases) in native Alaskans were 1.73 for men and 3.31 for women. The incidence of salivary gland cancer in these racial subgroups was, therefore, five times that of White American women. These workers also detailed the racial subgroups suffering from these tumours and found that among these native Alaskans, the majority were Yupic- or Inupiaq-speaking Eskimo and a minority were Athabaskan Indians who are a minority of the population there. Earlier, Hanji and Gohao (1983) in reporting nine cases and a review, estimated that for Eskimo populations in Greenland, northern Canada and Alaska, the incidence rate was 4.5 per 100,000 for males and 9.6 per 100,000 for females, and the rates for salivary gland cancer were therefore among the highest in the world.

The eight Chinese or Anglo-Chinese patients reported by Saw et al. (1986) had a mean age of 49.4 years (range 15-72 years) and males predominated in the ratio of 5:3. In the 14 Alaskan patients reported by Krishnamurty et al. (1987), the median age was 44 years for men and 39 years for women (range 17-70 years) and females predominated in the ratio of 11:4. Of 73 the patients reviewed by Ellis and Gnepp (1988), the age of affected patients ranged from 14 to 86 years, the mean age was 44 years and females predominated in the ratio of 1.5:1. Rarely, patients have had pre-existing or remnants of benign lymphoepithelial lesion, but only one patient (Delaney and Balogh, 1966) is known to have had Sjögren's syndrome. Overall, therefore, undifferentiated carcinoma with lymphoid stroma does not appear to be a sequel of benign lymphoepithelial lesion.

The exceptionally high incidence of otherwise rare tumours in mongoloid races in such widely disparate environments and of such different dietary habits, strongly suggests a genetic contribution to susceptibility. However, clustering of this tumour has been only recently reported among Eskimo families by Merrick et al. (1986) who reported cases in five sisters of two families. The first familial cases in Whites were reported by Autio-Harmainen et al. (1988) who described malignant lymphoepithelial tumours in both mother and daughter in a Finnish family with a dominantly inherited trait for trichoepithelioma.
Immunological findings

Immunological investigations have been carried out on a limited scale. Of 10 native Alaskans with these tumours, Krishnamurty et al (1987) found that none had SS-A or SS-B antibodies characteristic of Sjögren's syndrome, but two patients were SS-C (rheumatoid antinuclear antibody and reactive with extracts of Epstein-Barr virus-positive B-lymphocytes). Alaskans with either benign lymphoepithelial lesion or undifferentiated carcinoma with lymphoid stroma had titres of IgG antibodies to Epstein-Barr viral capsid antigen and to Epstein-Barr nuclear antigen, consistent with earlier Epstein-Barr viral infection. However, two patients showed a rise in titres of most Epstein-Barr viral antibodies with development of metastatic disease. By contrast, one patient with extensive metastases and two with spread to regional nodes showed no such rise in these antibody titres. Of eight patients reported by Saw et al (1986a), six had raised serum titres of IgA antibodies to Epstein-Barr viral capsid antigen.

Microscopy

The characteristic features are irregular, ill-defined islands of carcinomatous epithelium in a dense lymphocytic stroma (Fig. 7.103). The epithelial cells are pleomorphic, undifferentiated and often appear syncytial (Fig. 7.104). The nuclei are vesiculated, nucleoli may be prominent and there is variable mitotic activity. The stroma, by contrast, is lymphoplasmacytic and benign, but in high-grade tumours, lacks germinal centres. Saw et al (1986b) point out that reactive histiocytes can give the stroma a starry sky appearance.

Low-grade undifferentiated carcinoma with lymphoid stroma may be identifiable by more orderly arrangement of the tumour epithelium which sometimes shows palisading. Central necrosis and sometimes mitotic activity are also absent. The lymphocytic stroma may also be ductocentric and may show germinal follicles.

Low-grade undifferentiated carcinoma with lymphoid stroma may be identifiable by more orderly arrangement of the tumour epithelium which sometimes shows palisading. Central necrosis and sometimes mitotic activity are also absent. The lymphocytic stroma may also be ductocentric and may show germinal follicles.

These microscopic appearances are similar to, and may be indistinguishable from, those of the lymphoepithelial variant of nasopharyngeal carcinoma. The latter has an even higher in these racial groups, than the similar-looking salivary gland carcinoma and the possibility that a salivary undifferentiated carcinoma with lymphoid stroma is a metastasis from an occult nasopharyngeal carcinoma should therefore be ruled out (Saw et al, 1986a).

Behaviour and prognosis

These tumours are actively invasive and metastasize to regional lymph nodes and distant organs. Follow-up of 73 cases by Ellis and Gnepp (1988) showed that there had been an 18% recurrence rate. Fifty-seven per cent had spread to the regional lymph nodes, 23% had more distant metastases and 35% of patients died from their disease. In the small group of Alaskan natives investigated by Krishnamurty et al (1987) low-grade tumours were identified in 6 of the 14 with undifferentiated carcinoma with lymphoid stroma. None of the
six patients developed metastases and were alive 5-22 years after treatment; by contrast, all patients with high-grade tumours died from their tumour or its complications within 8 months to 5 years after treatment. The eight patients reported by Saw et al (1986b) were alive and well after periods of 7 months to 9 years, apart from one patient who died of unrelated infection. All of these patients had received radiotherapy after excision of the tumour.

**Treatment**

In view of the aggressive behaviour of high-grade undifferentiated carcinoma with lymphoid stroma, radical excision is required and the high frequency of spread to regional lymph nodes suggests that prophylactic neck dissection should be performed.

Radiotherapy may be used to supplement surgery and must be used if complete resection of the tumour is not possible. However, the tumour is not particularly radiosensitive and there is no certainty that such treatment prolongs survival.

**Note**

1. N. Kulschitzky (1856-1925), Russian histologist; imprisoned and forced by the Communists to make soap but escaped in 1918, by walking with his family from Kharkov to Sebastopol, and migrated to London.
Non-epithelial tumours of salivary glands are rare. They accounted for 4.5% of the material described by Seifert et al (1986) and 4.7% of the BSGTP material. As mentioned in Chapter 4, the most common types of non-epithelial tumours of salivary glands in adults are lymphomas. Some of these lymphomas are primary tumours whilst in others, the salivary gland mass is the initial manifestation of disseminated disease. Next in frequency is juvenile haemangioma; it is by far the most common salivary gland tumour of childhood and overall (with other types of vascular malformation) accounted for 52.5% of the series of 120 non-epithelial tumours (excluding lymphomas) of Seifert et al (1986). The next most common non-epithelial tumours in this series were lipomas (18.5%) and neural tumours (17.5%), while other benign mesenchymal tumours accounted in all for only 4.5%. Sarcomas formed 7.5% of this series and only isolated examples of the last two categories have been reported. They do not differ from their counterparts in other sites and the only important diagnostic consideration is to distinguish connective-tissue tumours from spindle cell myo-epithelial tumours.

**Haemangioma of the Parotid Glands**

Haemangiomas, or rarely lymphangiomas, may be present at birth, are most common before the age of 10 years and are exceedingly rare in adults.

**Clinical features**

Girls are affected more frequently than boys. The tumour forms a diffuse soft swelling of the parotid gland and if particularly widespread, may appear bluish. Rarely, the vascular channels can be so extensive as to form an arteriovenous shunt and there have been occasional reports of high output failure as a consequence. Other salivary glands are hardly ever involved.

**Microscopy**

The appearance is distinctive and consists in most cases of a multiplicity of capillaries, among which are isolated remnants of glandular tissue, particularly ducts (Fig. 8.1). In the rare angiomas of adults, thromboses can lead to phlebolith formation, which can also follow regression of haemangiomas in children.

Occasionally, these haemangiomas are partly or predominantly cavernous or are mixed haemangiomas and lymphangiomas. Some are highly cellular and their infiltrative appearance can mimic a malignant vascular tumour. Lymphangiomas, haemangiopericytomas and haemangioendotheliomas of the parotid glands have also been described. In patients with AIDS, Kaposi's sarcoma occasionally involves a salivary gland.
Behaviour and management

Spontaneous regression of juvenile haemangiomas is well recognized and operation should therefore be delayed if possible, until the age of about five years if the tumour shows no signs of regressing. The difficulties of surgery and the risk of damage to the delicate developing facial nerve are then less. Because of these problems, attempts have been made to reduce the bulk of large infantile haemangiomas, to delay surgery as long as possible, by such means as injection of sclerosing agents or cryosurgery. However, complications can outweigh any benefits. Irradiation is effective but its carcinogenic potential, in particular, rules out its use. Corticosteroids have been reported to control rapidly growing haemangiomas but this does not appear to have been widely confirmed.

Once operation has been decided on, total excision is curative but recurrence can follow incomplete removal. However, as mentioned earlier, avoidance of damage to the developing facial nerve is likely to be difficult.

Lymphangioma

Pure lymphangiomas of salivary glands are very uncommon. Even more rarely they can be very large, cause thinning of the overlying skin and may be fluctuant.

Unlike haemangiomas, lymphangiomas do not regress spontaneously and need to be excised. Aspiration cytology is helpful, but once the diagnosis has been confirmed, surgery is difficult and may have to be carried out in stages.

Embryoma (Sialoblastoma)

The variety of appearances is suggested by the names that have been given to these tumours. These include 'sialoblastoma' (Vawter and Tefft, 1966), 'embryoma' (Roth and Micheau, 1986), 'congenital basal cell adenoma', 'embryonal carcinoma' and 'congenital basal cell adenoma-adenoid cystic carcinoma' (Simpson et al, 1986).

Batsakis et al (1988) comment on the confusing nomenclature and suggest guidelines for the terminology of congenital and perinatal salivary gland tumours namely:

➤ Tumours indistinguishable from adult-type salivary gland tumours such as pleomorphic adenoma or undifferentiated carcinoma should be categorized accordingly.

➤ Tumours which have no adult counterparts should be termed 'embryoma' and subclassified as benign or malignant.

Batsakis et al (1988) emphasize that a property of embryonic tissue is infiltrative growth and that criteria for malignancy in an embryoma should include invasion of nerves or blood vessels, necrosis and greater atypia than expected of embryonic epithelium.
A sialoblastoma appears to have been first reported by Vawter and Tefft (1966) and described in detail by Taylor (1988). In the latter case, a large firm fixed mass extended from the mid-cheek to the tragus, deformed the otic canal and caused difficulties in delivery at birth. Facial palsy was associated. Computerized tomography scanning showed large feeder arteries from the left carotid and costocervical trunk. Batsakis et al (1988) also reported a case of a congenital parotid tumour and reviewed earlier reports. They noted that of 16 previously reported perinatal salivary gland tumours. Twenty-five per cent of these perinatal tumours were malignant. Apart from a single pleomorphic adenoma, all of these tumours shared a structure suggestive of embryonic salivary gland epithelia at varying stages of differentiation in a loose mesenchymal stroma. Harris et al (1990), in another review of the subject, also reported a congenital submandibular gland tumour which had grown since birth, in a 10-month infant.

Microscopy

The tumour reported by Taylor (1988) consisted predominantly of uniformly sized cells with relatively little amphophilic cytoplasm and some mitotic activity. The cells were mostly in solid lobules but with some duct-like structures budding from them. In other areas, more pronounced ductal differentiation and rare foci with a cribriform pattern were evident. The tumour reported by Batsakis et al (1988) also consisted predominantly of small, dark epithelial cells in the form of solid masses and ducts, but without acinar differentiation. Mitoses were frequent in the undifferentiated areas which had an embryonic appearance. The stroma was loose and vascular.

The tumour reported by Harris et al (1990) was circumscribed and consisted of aggregates of basaloid cells, ducts, acini and associated myoepithelial cells (Fig. 8.2). The acinar cells contained secretory granules which stained positively with periodic acid-Schiff. The epithelial structures were surrounded by a moderately vascular stroma containing nerve fibres. Overall, there were many features in common with fetal salivary tissue, but it was difficult to be certain whether it was a neoplasm or hamartoma.

It seems, therefore, that most congenital salivary gland tumours, apart from haemangiomas, can justifiably be designated 'embryoma'. Though there are some variations, these tumours have many microscopic features in common, namely, solid masses of small, dark cells with variable mitotic activity and some duct differentiation in a loose mesenchymal stroma. These appearances may be mistaken for a basal cell adenoma or adenoid cystic carcinoma.

Behaviour and prognosis

As an example of the behaviour of a malignant embryoma, the example reported by Taylor (1988) was excised 10 after birth but recurred six months later. A further operation at 13 months of age did not allow total excision because of extension into the skull. Radioactive gold implants were inserted but were followed by two further recurrences in the succeeding 30 months. However, there were no signs of metastases.
Some of these embryomas are benign, despite appearances suggesting invasion, but others are malignant as shown by both the microscopic features and behaviour. The treatment must therefore be planned accordingly but clearly this may present considerable difficulties.

**Mixed Hamartomas of Salivary Glands**

Some congenital tumours previously categorized as neoplasms have been found on further examination to be hamartomas with proliferation of all major components of normal salivary gland tissue, but particularly, ducts.

**Other Salivary Gland Tumours in Childhood**

In addition to embryomas and hamartomas, any of the salivary gland neoplasms of adult life can occasionally be seen in childhood. Seifert et al (1986) on the basis of earlier reports suggested that 3.5-5% of salivary gland tumours were in children up to the age of 16 years, but included in this estimate the vascular tumours described earlier.

Shikhani and Johns (1988), in a review of the English-language literature, concluded that 472 cases had been reported and presented 21 new ones (excluding vascular tumours), seen over a 30-year period. These 21 cases represented 3.7% of all 575 salivary gland neoplasms seen during this period. However, for this series, an upper age limit for childhood was set at 20 years and only 12 patients were < 17 years old. Three of these 21 tumours were mucoepidermoid carcinomas and the remainder (18) were pleomorphic adenomas. All of the latter were treated by local excision or superficial parotidectomy, eight recurred and four were left with facial-nerve weakness. The high incidence of facial nerve injury illustrates the surgical difficulties presented by parotid gland tumours in children. Of the three mucoepidermoid carcinomas, one was treated by total parotidectomy alone and showed no signs of recurrence after four years. The other two had local excisions followed by radiotherapy; one of these was still free of disease 25 years later.

Shikhani and Johns (1988) analyzed the relative incidence of different histological types among 472 previously reported and their own cases of childhood salivary gland tumours. No fewer than 50% were malignant and confirmed that malignant salivary gland tumours were relatively considerably more frequent than in adults. These malignant tumours were mainly in older children and more frequently in the parotid glands.

Of the 229 benign tumours, pleomorphic adenomas formed 86.6%. Of the 243 malignant tumours, mucoepidermoid carcinomas comprised 49.6%, acinic cell carcinomas 12.2%, undifferentiated carcinomas 8.9% and adenoid cystic carcinomas 6.5%. They also summarized the treatment and outcome of 272 cases where sufficient data were available and noted that the recurrence rate of pleomorphic adenomas after enucleation was > 39% but 19.5% after superficial parotidectomy. They considered that these exceptionally high recurrence rates were probably a reflection of the difficulties of operating on small glands. Two of these recurrent tumours underwent transition to highly aggressive carcinomas. Overall, 32 patients (11.4%), including one who had had a pleomorphic adenoma, died from their tumours.
Callender et al (1992) reviewed the results of surgery of 29 non-vasoformative salivary gland tumours in children aged 3-16 years. Of the eight pleomorphic adenomas, there were no recurrences after parotidectomy after a mean follow-up period of 15.9 years. Mucoepidermoid carcinoma was the most common of the malignant tumours and of 21 of the latter, 17 remained free from disease after surgery for periods of between 3.5 and 30.5 years (mean 13.6 years).

Lack and Upton (1988) also reviewed their experience of salivary gland tumours (including vascular malformations) in children and described the findings in 80 patients below the age of 18 years. Of the 25 epithelial tumours, 10 were pleomorphic adenomas, six were mucoepidermoid tumours and two were congenital carcinomas. Of the 55 non-epithelial tumours, 46 were vascular; six were neural and frequently associated with neurofibromatosis.

In summary, then, the most common salivary gland tumours of early infancy or the neonatal period are haemangiomas. In older children, the most common type of epithelial tumour is the pleomorphic adenoma but approximately 50% of tumours are malignant. Of the latter, mucoepidermoid carcinomas are most frequent. Enucleation or superficial parotidectomies of pleomorphic adenomas have been followed by exceptionally high recurrence rates and, in a few cases, malignant change. Shikhani and Johns (1988) recommend total parotidectomy for pleomorphic adenomas in children, but the chances of damaging the facial nerve are high.

Neurilemmomas and Neurofibromas

Neural tumours appear to be the most common connective-tissue tumours in salivary glands in adults; they formed 8% of the non-epithelial tumours in the BSGTP material and 17.5% of the material presented by Seifert et al (1986).

Clinically, neural tumours are not distinguishable from other benign tumours of salivary glands. The only condition likely to suggest their nature is when Von Recklinghausen's disease (neurofibromatosis type I) is present.

Microscopy

In the BSGTP material, of 11 nerve sheath tumours, three were neurilemmomas, four neurofibromas and four plexiform neuromas. The patients with neurilemmomas or neurofibromas were all > 30 years while all those with plexiform neuromas were < 18 years and were found to have neurofibromatosis (Palmer et al, unpublished data).

In a typical neurilemmoma with Antoni A tissue of compact masses or whorls of Schwann cells with nuclear palisading, the diagnosis should be obvious (Fig. 8.3). Foci of hyalinization which may undergo calcification or Verucay bodies are also distinctive. Antoni B tissue has a more nondescript appearance and consists of a loose mass of irregularly arranged elliptical or spindle cells in a myxoid matrix. Mast cells may be prominent and are a clue to the diagnosis. However, distinction from well-differentiated neurofibrosarcomas can be difficult.
Solitary neurofibromas are rare in any site and should lead to the suspicion that the patient has neurofibromatosis. The appearances are variable but most characteristically consist of irregularly interlacing bundles of spindle-shaped cells with bent nuclei separated by fine, sinuous collagen fibres. These cells are sometimes in a myxoid matrix and either component may predominate. Other cells, in addition to mast cells, which may be present are occasional inflammatory or xanthoma cells, or squamous epithelial inclusions. The possible role of mast cells in nerve sheath tumours, including neurofibromatosis, has been reviewed by Claman (1987).

Plexiform neurofibromas consist of spindle cells with myxoid areas mixed with normal nerve fibres in a highly irregular pattern. They may contain Wagner-Meissner corpuscles and as indicated earlier, are frequently associated with or possibly pathognomonic of peripheral neurofibromatosis (Fig. 8.4).

Neurofibrosarcomas or malignant schwannomas are particularly rare in salivary glands; they may arise de novo or from a neurofibroma of Von Recklinghausen's disease. Seifert et al (1986) mention only two cases among 120 non-epithelial tumours. Like neurofibrosarcomas in other sites, they may be difficult to distinguish microscopically from other soft-tissue sarcomas but frequently consist of plump spindle cells, typically with sinuous or bent nuclei, in a swirling pattern of fibrous stroma more irregular than that of fibrosarcomas. In some cases, the tumour cells may have an epithelioid appearance and form nests resembling an amelanotic melanoma. Occasionally heterotopic tissues such as cartilage or muscle may form. Myxoid areas or others resembling Antoni A tissue are suggestive, but the diagnosis can be confirmed if an origin from a branch of the facial nerve or a pre-existing neurofibroma can be seen. Staining for S-100 protein may be positive but sometimes electron microscopy is needed to demonstrate an origin in Schwann cells.

**Treatment**

Most neural tumours are recognized only after parotidectomy. Rarely, a neural tumour arises from a major branch of the facial nerve and it may be difficult to resect completely and restore nerve continuity. In neurofibromatosis, surgery is likely to be needed to confirm the diagnosis, or if the tumour is large, excision is necessary for cosmetic reasons.

In the case of neurofibrosarcoma, total parotidectomy is necessary and followed by radiotherapy. Insufficient data on the prognosis of these tumours are available, but overall, it is poor, particularly when associated with neurofibromatosis. Spread is mainly to the lungs and rarely to lymph nodes, except in the later stages when metastases become widespread.

Five-year survival rates may range from 25 to 75% according to stage and other variables, but if associated with neurofibromatosis, survival is likely to be only half as good as for a comparable solitary tumour.

**Lipomas**

Lipomas form virtually exclusively in the parotid glands which have a significant fat content as a normal feature. In the BSGTP material they formed 4.3% of the non-epithelial tumours. As described below, liposarcomas are particularly rare in salivary glands.
Lipomas affect adults, particularly males. If sufficiently extensive, a parotid gland lipoma may feel soft.

**Microscopy**

Salivary gland lipomas, like those in other sites, consist of fat globules and mature adipocytes, and resemble normal fat. They are distinguishable from lipomatosis only in that a capsule may be discernible.

**Treatment**

Excision of the tumour, the nature of which is likely to become apparent at operation, us curative and there should be no hazard to the facial nerve.

**Other Soft-Tissue Tumours**

Isolated examples of other non-epithelial tumours of salivary glands have been reported. Seifert et al (1986) mention fibroma, osteochondroma, granular cell tumour, malignant fibrous histiocytoma, rhabdomyosarcoma and angiosarcoma. In the BSGTP material, there have been 163 non-epithelial tumours (5% of all salivary gland tumours or 4% if lymphoepithelial lesions are excluded). In an analysis of the AFIP material, Auclair et al (1986) found that sarcomas formed 1.5% of all salivary gland tumours but this figure probably exaggerates their true incidence, because of the greater numbers of more unusual types of tumours referred to that Institute. Among more than 3500 salivary gland tumours in the BSGTP material, sarcomas formed only 0.3% and a somewhat similar proportion appeared in the Hamburg Salivary Gland Tumour Register (Seifert et al, 1986). Auclair et al (1986) also reviewed 33 previously reported cases and the rarity of sarcomas of salivary glands is suggested by the series reported by Farhood et al (1990) where, among 176 soft-tissue sarcomas of the head and neck, 2% were stated to have arisen in the parotid region, but none appeared to have arisen in the parotid or any other salivary gland.

In the material analyzed by Auclair et al (1986), malignant schwannoma and undifferentiated sarcomas were the most common types, followed by fibrosarcoma, malignant fibrous histiocytoma and rhabdomyosarcoma. Ellis and Gnepp (1988) point out that in the past, rhabdomyosarcomas have been the most frequently reported sarcomas of salivary glands, but that this may be misleading in that improved diagnostic methods, especially immunocytochemistry, have shown that many of these poorly differentiated tumours should be recategorized. As a result, Auclair et al (1986) were able to reclassify 12 of 27 tumours. Five were found to stain for keratin and five to react strongly for S-100 protein and were therefore recategorized as spindle cell carcinomas and malignant melanomas, respectively. In addition, one fibrosarcoma was recategorized as an angiosarcoma by its reaction for factor VIII-related antigen. Another fibrosarcoma had some reactivity for S-100 protein and was recategorized as a malignant schwannoma. Renick et al (1988) have also reported an embryonal rhabdomyosarcoma of the parotid gland and in a review of earlier reports found 12 examples of these tumours.
Ellis and Gnepp (1988) also point out that, compared with the rest of the body where malignant fibrous histiocytomas and liposarcomas are the most common types of sarcoma, they appeared to be underrepresented in salivary glands in the AFIP material and no cases of liposarcoma were found there or in a review of the literature. More recently, Luna et al (1991) reported 11 primary salivary gland sarcomas and reviewed 74 previously reported cases. Of the total of 85 sarcomas, the single most frequent types were rhabdomyosarcomas (18 cases) and malignant fibrous histiocytomas (15 cases). Eight tumours were of unspecified type but reports of two cases of liposarcoma were found.

Kaposi’s sarcoma involving both parotid glands has been reported by Yeh et al (1989) in a patient with AIDS.

Clinically, 88% of the sarcomas reviewed by Ellis and Gnepp (1988) were in the parotid glands. They were found in patients with a mean age of 40 years but the range was from 1 to 91 years. The age of presentation was, overall, somewhat earlier than for soft-tissue sarcomas in other sites.

Most of these tumours formed painless swellings, but growth was rapid and the average history was only four months. Haematogenous spread was considerably more common than nodal spread.

**Behaviour and management**

Because of the rarity of these tumours, it is impossible to suggest a definitive plan of management other than that radical parotidectomy is the first requirement and other treatment does not differ from current protocols for such tumours in other sites. The value of chemotherapy, for example, is difficult to assess. As adjunctive treatment of rhabdomyosarcomas in particular, it appears to have improved the prognosis, but in their review, Ellis and Gnepp (1988) found little evidence for the value of either adjunctive radiotherapy or chemotherapy for salivary gland sarcomas. Only 40% of the 33 patients followed by Auclair et al (1986) were free of tumour and one-third of the cases died from their disease. The mean survival time of the latter was only 2.6 years and only one patient survived for more than five years. Of the 11 patients reported by Luna et al (1991), seven died from their disease within periods of six months to four years: three patients had no evidence of disease after periods of five to nine years.

It might be expected that salivary gland sarcomas would be recognized at an unusually early stage because of their relatively superficial site, and therefore have a more favourable prognosis. However, the survival figures suggest that is not the case and any benefit from early recognition may be nullified by their proximity to vital structures.

**Nodular Fasciitis**

In the body as a whole, nodular fasciitis is one of the most common causes of tumour-like fibrous masses. It is a benign proliferative lesion but its rapid growth and microscopic appearances cause it to be readily mistaken for a sarcoma. Nodular fasciitis particularly affects the upper extremities in adults and is common in the head and neck region only in children.
Nodular fasciitis has been reported as a rare cause of parotid tumours by Fischer et al (1989) who reviewed previous reports. However, Enziger and Weiss (1995) point out that some 50% of cases in several reports had originally been mistaken for sarcomas, so that it is possible that some of the earlier reported sarcomas of salivary glands might now be recategorized as nodular fasciitis.

**Microscopy**

The mass is non-encapsulated and may be intermingled with the gland parenchyma at its periphery. It consists of short irregular bundles of immature fibroblasts, many of which show mitotic activity. There is an abundant myxoid matrix, which can spread the fibroblasts to form feathery patterns and contains scattered inflammatory cells. Later the lesion may shrink as a result of fibrosis or undergo cystic change.

Nodular fasciitis must be distinguished from a fibrosarcoma to avoid unnecessarily extensive surgery. Points which help to make this distinction are that in fibrosarcomas, the neoplastic fibroblasts are closely packed and lack a conspicuous matrix. These cells form streaming, interlacing bundles which characteristically appear as herring-bone patterns. Their nuclei are also more pleomorphic and mitoses may be atypical.

Nodular fasciitis can, if necessary, be distinguished from spindle cell myoepitheliomas by failure of its fibroblasts to stain for keratins or S-100 protein.

**Behaviour and management**

As mentioned earlier fasciitis, despite its rapid initial rate of growth and microscopic appearances, is benign and self-limiting. In most cases the lesion will have been treated as a tumour and the diagnosis made postoperatively. It is important therefore not to extend the original excision but to keep the patient under review.

**Solitary Plasmacytoma of Salivary Glands**

Several cases of this tumour have been reported. El Naggar et al (1991) described a new case with typical crystalline inclusions and found reports of eight previous cases, though there are several others.

Patients are typically of middle age or over and males predominate in the ratio of > 2:1 but the tumour presents no distinctive clinical features.

**Microscopy**

The neoplastic plasma cells may be well or poorly differentiated but pyroninophilia and immunoglobulin or light-chain production can be readily demonstrated in them. A monoclonal component in the serum is rarely found in solitary soft-tissue plasmacytomomas and electrophoresis may not be of value in confirming the diagnosis.
Treatment

In the absence of a clinical diagnosis, the tumour is likely to have been excised, but radiotherapy is very effective and should certainly be given if excision has been incomplete or if there is a recurrence. The prognosis is considerably better than for multiple myeloma but the disease can progress to multiple myeloma within a few years or only after several decades.

Giant-Cell Tumours of Salivary Glands

Very rarely, salivary gland tumours consisting largely of osteoclast-like giant cells are seen, as may happen in other organs, notably the thyroid. Among them, the most readily identifiable are giant-cell fibrous histiocytomas. The nature of others is more difficult to define and they probably form a heterogeneous group.

Ellis and Gnepp (1988) reviewed these tumours and describe them as consisting of osteoclast-like giant cells, containing 5-30 nuclei and acidophilic cytoplasm, in a stroma of mononuclear cells, but the appearances are variable (Fig. 8.5). In particular, the mononuclear cells range from a uniform bland appearance to atypia with nuclear pleomorphism and hyperchromatism. In two of the three tumours described by Eusebi et al (1984), there was osteoid formation and bony trabeculae in one of them. One of those containing osteoid abutted on, or was admixed with, a carcinoma arising in a pleomorphic adenoma. Of the four additional cases described by Ellis and Gnepp (1988), two had osteoid and bone formation. Two of these tumours were circumscribed and the others were infiltrative.

In view of the rarity of these tumours and the short periods of follow-up, it is impossible to generalize about treatment or prognosis, but it is likely that their behaviour will correlate to some extent with the degree of atypia and local signs of aggressiveness.

So-Called 'Benign Lymphoepithelial Lesion'

The term 'benign lymphoepithelial lesion' was introduced by Godwin in 1952 to describe lymphoid infiltration of salivary gland tissue associated with acinar atrophy but with proliferation of ductal elements. Mason and Chisholm (1975) give a useful account of the historical background to the ideas about the nature and confusing terminology of these lesions since they were first reported by Mikulicz in 1892. Salivary lymphoepithelial lesion has been discussed in relation to Sjögren's syndrome in Chapter 4.

The term 'benign lymphoepithelial lesion' is distinctly misleading in view of the risk of lymphoma in these patients and is only used here as the traditional term in the UK. Some prefer the term 'autoimmune sialadenitis' whether or not it is associated with clinical symptoms of Sjögren's syndrome. Another term, 'myoepithelial sialadenitis' (MESA) is widely favoured even though, as mentioned earlier, myoepithelial cell proliferation is not a feature of this disease. More recently, Batsakis (1987) has suggested the noncommittal term 'lymphoepithelial sialadenopathy' for lesions which can range from limited salivary gland diseases to Sjögren's syndrome with widespread systemic manifestations, and this may be a more appropriate term.
Clinical features

Benign lymphoepithelial lesion, as seen by the surgeon, appears as a diffuse swelling of the parotid gland in the great majority (80%) of cases; in the BSGTP material, 20% were bilateral. The swelling is typically firm but not fixed to skin or deep tissues but in about 40% of patients is painful.

In 36 patients with the primary diagnosis of benign lymphoepithelial lesion, reported by Gleeson et al (1986b), only 50% had or developed Sjögren's syndrome, or related autoimmune disease, most commonly, rheumatoid arthritis, but the period of follow-up was limited. Nevertheless, like Sjögren's syndrome, 83% of these patients were women and the majority were > 50 years of age. Further, patients will frequently not volunteer that they have dry mouth or eyes or both, or apparently not regard these symptoms as abnormal (Chapter 5). Alternatively, salivary or lacrimal secretion may be impaired but asymptomatic as also discussed earlier.

Microscopy

The salient features are a lymphoplasmacytic infiltrate, which is initially periductal but extends and progressively replaces acinar tissue. Ducts are disrupted but tend to persist and some of the ductal epithelium proliferates to form so-called 'epimyoepithelial islands' (Fig. 8.6). The latter is a misnomer in that electron microscopy and immunocytochemistry have shown that myoepithelial cells are absent (Fig. 8.7).

Epimyoepithelial islands are irregular in shape but sharply demarcated from the surrounding lymphocytes. Their epithelium appears squamous; they are usually solid, but sometimes contain minute lumens and are surrounded by a conspicuous basement membrane. The latter may be hyalinized and some of this hyaline material may be enclosed within the islands (Figs 8.8 and 8.9). Occasional small ducts may also persist, at least in the penultimate stages, and may rarely form minute cysts.

The final picture is one of total replacement of acinar tissue by a dense lymphocytic infiltrate in which epimyoepithelial islands are scattered.

The lymphocytic infiltrate is confined within the capsule of the gland, is polyclonal and includes variable numbers of plasma cells. Germinal centres may form and occasionally become so numerous as to give an appearance superficially resembling a follicular lymphoma.

Diagnosis

Benign lymphoepithelial lesion should be suspected in patients with a tumour-like parotid swelling with any of the following characteristics or associations:

➤ Diffuse swelling of the parotid gland particularly in women of middle age or older.
➤ Bilateral parotid swellings.
➤ Salivary gland swellings in patients with:
rheumatoid arthritis
any other connective tissue disease or related autoantibody findings (Table 4.3);
dry mouth or eyes or other dry gland complications (Table 4.2);
microscopic changes of Sjögren's syndrome in a minor (labial) gland biopsy.

Management

In addition to the medical management of Sjögren's syndrome or associated disease, the two major problems are the risk of lymphomatous change and the operative difficulties in excising benign epithelial lesions. The risk of lymphoma is greatly increased in benign lymphoepithelial lesion, particularly when associated with rheumatoid arthritis, but it may be difficult to recognize lymphomatous change in a limited area of this lymphoproliferative lesion.

In most cases, a preoperative diagnosis cannot be made with certainty, but even if a benign lymphoepithelial lesion is suspected this hardly alters the surgical approach except in so far as it is a warning that it is likely to be difficult. Because of the risk of lymphomatous change, it is important that the lesion should be removed in its entirety if only for adequate microscopic examination. The surgical problem is that the lesion is diffuse and obliterates the normal planes of cleavage protecting the facial nerve and its branches, which as a consequence, are very difficult to define.

Even when the patient is known to have Sjögren's syndrome, the treatment of persistent parotid swelling, particularly when painful, does not differ. Treatment with corticosteroids may relieve the pain but their long-term use is undesirable. In any case, since the parotid glands of these patients are non-functional and are a potential site for lymphomatous change, parotidectomy is the treatment of choice.

Postoperative histological confirmation of the diagnosis of benign lymphoepithelial lesion should also not lull the surgeon into a false sense of security. Because of the increased risk of lymphoma, prolonged follow-up is essential, and further investigation should be initiated at the slightest suggestion of any change in the glands or lymph nodes.

Even if the diagnosis of benign lymphoepithelial lesion is made postoperatively, investigation or referral to a physician is desirable to treat or exclude any autoimmune disease or complications.

Benign Lymphoepithelial Lesion and Sjögren's syndrome

Although it is probable that there is no real distinction between these diseases, the fact remains that many surgeons, in particular, remain uncertain about their nature.

Though the microscopic features of benign lymphoepithelial lesion are the same as those of well-established Sjögren's syndrome, it was suggested by Mason and Chisholm (1975) that these are separate entities, and clearly, many still believe this to be the case. The difficulty is created by the fact that Sjögren's syndrome is not frequently associated with salivary gland swelling and that salivary function or autoimmune disease is frequently not considered when the tumour-like mass of benign lymphoproliferative lesion is first seen. This
is confirmed by Ostberg (1983) who investigated 19 patients in whom the diagnosis of benign lymphoepithelial lesion had been made, and found that 84% of them had symptoms or immunological abnormalities of Sjögren's syndrome. Gleeson et al (1986b), also found that most cases of benign lymphoproliferative lesion had been treated as tumours without investigation of the possibility of autoimmune disease. As recently as 1989, Pall commented on the lack of awareness of primary Sjögren's syndrome. Even if Sjögren's syndrome is suspected, the diagnosis may not be easy, as discussed earlier (Chapter 5).

In practice, therefore, there are two groups of patients, distinguished mainly by their mode of presentation. The first have clinical manifestations of Sjögren's syndrome and are seen by physicians. In these patients, salivary gland swelling rarely warrants excision. The second group of patients have a tumour-like salivary-gland swelling, are referred to surgeons, and the possibility of Sjögren's syndrome is not considered. The enlarged parotids are therefore excised. However, it seems likely that if such patients were fully investigated, most (if not all of them) would be found to have Sjögren's syndrome in complete or incomplete form.

Lymphoma in Benign Lymphoepithelial Lesion or Sjögren's syndrome

As mentioned earlier, lymphomatous change in benign lymphoepithelial lesion is a recognized risk. In addition, there is also an increased risk of extrasalivary lymphomas in Sjögren's syndrome and related connective-tissue diseases, particularly rheumatoid arthritis, whether or not they are associated with benign lymphoepithelial lesion. Estimates of the level of risk vary widely. Symmons (1984) for example reported lymphomas in 2.2% of 489 patients with rheumatoid arthritis after a mean interval of 11.8 years, but in such connective-tissue diseases, salivary gland lymphomas are not necessarily secondary to Sjögren's syndrome. Among the 38 lymphomas involving salivary glands reported by Colby and Dorfman (1979), where a clinical history was available, five patients had arthritis or were rheumatoid-factor positive and four others had Sjögren's or sicca syndrome. Of seven lymphomas developing in benign lymphoepithelial lesion reported by Gleeson et al (1986), there was a history of rheumatoid arthritis in two, but none of Sjögren's syndrome. Hyman and Wolff (1976) reported 33 new cases of which four had arisen in benign lymphoepithelial lesions, whilst Colby and Dorfman (1979) reported 59 new cases, seven of which contained areas which resembled benign lymphoepithelial lesion. Shin et al (1991) have also noted a strong association between the recently recognized entity, monocytoid B-cell lymphoma and Sjögren's syndrome.

Of 36 cases of benign lymphoepithelial lesion accessioned by the BSGTP between 1971 and 1984, 14% were found to have lymphomatous change in the lesion, while three others, among 24 available for follow-up, developed systemic lymphomas in a mean period of 3.8 years. Earlier, Schmid et al (1982) had reported 26 lymphomas arising in benign lympho-epithelial lesion as well as 25 primary lymphomas which had arisen in previously normal glands, while more recently, Seifert et al (1986) has reported that 23% of salivary gland lymphomas in his series had arisen in benign lymphoepithelial lesion ('myoepithelial saladenitis') and this closely correlates with the 22% of malignant lymphomas associated with benign lymphoepithelial lesion in the series reported by Gleeson et al (1986b). Shin et al (1991) also noted the high frequency of association between Sjögren's syndrome and monocytoid B-cell lymphomas which are now accepted as being MALT lymphomas.
Undoubtedly, therefore, the risk of salivary gland lymphomas is significantly raised in benign lymphoepithelial lesion and particularly when associated with rheumatoid arthritis.

The possibility that lymphomatous change may have taken place in a benign lymphoepithelial lesion must always be considered and should not be dismissed because of persistence of, for example, epimyoepithelial islands (Fig. 8.10).

The persistence of epimyoepithelial islands or of germinal centres, in salivary gland lymphomas is well recognized (Fig. 8.11). Among 59 salivary gland lymphomas, either primary or secondary, reported by Colby and Dorfman (1979), for example, epimyoepithelial islands were found in no fewer than 14, despite the fact that few of them showed unequivocal signs of having originating in benign lymphoepithelial lesions. The diagnosis of lymphoma, therefore, depends on recognizing its cytological characteristics, in particular the more homogeneous cellular picture, and alternatively or in addition, signs of invasion (such as obliteration of interlobular septa or capsule, or both) or destruction of tissues such as nerves. In addition, immunostaining to show monoclonal immunoglobulin production is helpful as emphasized by Schmid et al. (1982), and may be conclusive.

The incidence of lymphoma in salivary lymphoepithelial lesion or Sjögren's syndrome may be ≥ 20% as reported by Gleeson et al (1986a) in a study of 36 cases. Takahashi et al (1992) found that in 32 salivary gland lymphomas the initial diagnosis had been myoepithelial sialadenitis in nine cases. Lymphoma is typically a complication of long-standing disease and is therefore more likely to be seen in the elderly, particularly women. There is also a greater risk of lymphoma in patients with connective-tissue diseases, particularly rheumatoid arthritis, as mentioned earlier.

Lymphomatous change may be difficult to recognize among the lymphoproliferation characteristic of these diseases. Persistence of epimyoepithelial islands or of germinal centres does not preclude its presence. It is indicated by cytological features of malignancy, signs of invasion and destruction of adjacent tissues. A more sensitive indicator is provided by evidence of expansion of a monoclonal B-cell population. Schmid et al. (1982), for example, considered areas of monotypic B-cell proliferation to represent lymphomatous change in Sjögren's syndrome. Fishleder et al. (1987) and Freimark et al. (1989) also proposed that foci of monoclonality represented 'prelymphomatous change'. Even in histologically benign lesions, Falzon and Isaacson (1991) have argued that a monoclonal B-cell population precludes the diagnosis of benign lymphoepithelial lesion. Moreover, immunoglobulin gene rearrangement is such a population may be identical to that in extrasalivary lymphomas in the same patient. Extensive areas of monoclonality are detectable by simple immunostaining but a limited area may be masked by the general polyclonal infiltrate and a more sensitive method is required.

Jordan et al. (1995) have pursued the detection of monoclonality in salivary lymphoepithelial lesions using the polymerase chain reaction as well as immunohistochemistry and in situ hybridization, and reviewed previous work in this field. These methods in combination identified light-chain restriction in 77% (17 of 22 cases). The single most sensitive method was by the polymerase chain reaction which detected B-cell monoclonality in 68% of cases. Seven sequential biopsies were available from other sites and six of them also showed B-cell monoclonality. By contrast, Pablos et al. (1994) found by the polymerase chain reaction, clonal expansion of the heavy-chain immunoglobulin gene in the labial
salivary glands of 13 patients with Sjögren's syndrome, but none developed a lymphoma within a mean period of follow-up of four years after biopsy. A B-cell lymphoma developed in another patient but the clonal rearrangement of the tumour differed from the predominant rearrangement in the labial salivary glands at that time.

It may be noted that lip biopsies are frequently carried to confirm the diagnosis of Sjögren's syndrome and they can be used for quantification of kappa to lambda ratios and may therefore be valuable for early detection of malignant lymphoproliferation. Thus Speight et al (1994) have shown that lymphomatous change in Sjögren's syndrome can be predicted by in situ hybridization for kappa and lambda light-chain mRNA in labial salivary glands. Of seven cases showing light-chain restriction, four developed low-grade mucosa-associated lymphoid tissue (MALT) lymphomas while a fifth died from disseminated lymphoma. They concluded that when lymphoma develops in Sjögren's syndrome, lymphoma cells may disseminate to labial salivary glands before the onset of symptoms. Jordan et al (1995) have also shown by in situ hybridization in 70 labial salivary gland biopsies, that 18.6% showed light-chain restriction. Subsequently 30.7% of these patients were found to have extrasalivary lymphomas within a follow-up period of 18-156 months.

Although small areas of monoclonality can be identified by molecular techniques, they are so sensitive that the significance of positive findings is as yet controversial.

It would be surprising if light-chain restriction in 77% of salivary lymphoepithelial lesions, as reported by Jordan et al (1995) represented early lymphomatous change in every case. Though detection of a small focus of monoclonality may be a controversial as an indication of the presence or likelihood of lymphoma, it should at least serve as a warning of the possibility and the need to keep the patient under observation. In view of the age of most affected patients, lymphoma may not develop within the patient's lifetime, but expansion of a monoclonal B-cell population in salivary lymphoepithelial lesion must be regarded with some anxiety.

Kassan et al (1978) quoted a 40-fold increased risk of lymphoma in Sjögren's syndrome compared with the general population but many of these lymphomas were more frequently extraglandular. However, in view of the findings of Falzon and Isaacson (1991) it seems possible that many of these may have been MALT lymphomas which homed from areas of light-chain restriction in salivary lymphoepithelial lesions.

The fact that salivary lymphoepithelial lesions, rheumatoid arthritis, other connective-tissue diseases and, particularly, Sjögren's syndrome are more common in women may explain the higher incidence of salivary gland lymphomas in females in most series.

**Primary Lymphomas of Salivary Glands**

Primary lymphomas of salivary glands are rare and, for example, were not described by Foote and Frazell (1954) in their monograph on salivary gland tumours. Lymphomas are also mentioned only as a complication of benign lymphoepithelial lesion by Thackray and Lucas (1974) in their data based on over 700 salivary gland tumours. Nime et al (1976) could find reports of only 29 cases of adequately documented primary salivary gland lymphomas and only a single example, among 2636 lymphomas (all sites), in three earlier reports. Of 473
Lymphomas (all sites), in three earlier reports. Of 473 lymphomas reviewed by Anderson et al. (1982), the great majority (316) were in lymph nodes and only one was known to have been in a salivary gland. Ellis and Gnepp (1988) have reviewed earlier reports of salivary gland lymphomas and noted that > 400 had been accessioned, but it was rarely possible to determine what proportion of them were primary tumours of salivary glands. The main reports of series of salivary gland lymphomas have been mentioned earlier, in relation to benign lymphoepithelial lesion.

Lymphomas found in salivary glands can be of different origins and present specific problems for both clinician and pathologist if the patient is not already known to have disseminated disease. Otherwise, the diagnosis is likely to be made only after excision and histological examination.

Since lymphomas are far more commonly nodal than extranodal, it seems probable that salivary gland lymphomas most frequently arise in intra- or juxta-glandular nodes and though they may then extend into the glandular parenchyma, the possibility that they are manifestations of disseminated disease, must be excluded. Of 59 salivary gland lymphomas described by Colby and Dorfman (1979), for example, 37 patients had disseminated disease and in 11 of these the diagnosis had already been established. In the material described by Seifert et al. (1986), 30% of 139 non-Hodgkin lymphomas of salivary glands were secondary to systemic spread. In many cases, however, destruction of the nodal architecture may make it impossible to be certain whether the tumour has arisen in an intra- or periglandular lymph node, but it is also possible for true extranodal lymphomas to develop in the parenchyma or as a result of lymphomatous change in benign lymphoepithelial lesion.

In addition, salivary gland lymphomas have been reported in patients with AIDS. Lymphomas of the head and neck region are considerably more common than in a non-infected population, and among the lymphomas in patients at high risk of, or with AIDS, 2 of 21 lymphomas in the series reported by Ioachim et al. (1988) and 2 of 31 in the series reported by Egeter and Beckstead (1988) were in salivary glands. The mean age of such patients is lower than for similar tumours in non-infected patients and all the patients in these reported series were males.

If therefore, these series are representative, then the incidence of salivary gland lymphomas, in association with HIV infection, appears to be high.

Yet another possibility is that of lymphoma developing in Warthin's tumour, but this is remarkably rare as discussed later. In summary, therefore, lymphomas in salivary glands can arise:

➤ as the first manifestation of disseminated disease;
➤ in juxta- or intraglandular lymphoid tissue;
➤ in the gland parenchyma;
➤ in benign lymphoepithelial lesion or Sjögren's syndrome;
➤ in association with other connective-tissue disease, particularly rheumatoid arthritis;
➤ as a complication of HIV infection; and
➤ rarely in Warthin's tumour.
Clinical aspects

Partly because of these variables, and because it is frequently unclear from reports whether a salivary gland lymphoma has arisen there or is secondary to disseminated disease, the incidence of primary salivary gland lymphomas is uncertain.

In the series of Seifert et al (1986) of 2913 salivary gland tumours, 4.5% (approximately 8% of all malignant salivary gland tumours) were lymphomas, while in the BSGTP series of 3500 salivary gland tumours, 2.4% were lymphomas.

In most series, the parotid gland has been the most frequent site. In the series of Seifert et al (1986), 60% were in the parotids whilst in the BSGTP material 50% were in those glands. The submandibular gland accounts for 15-20% and the remainder are in the minor glands, particularly of the palate. By contrast, in the series of Seifert et al (1986), Hodgkin's disease affected the submandibular gland (or more strictly, the juxtaglandular lymph nodes) slightly more frequently than the parotid gland. This is merely a reflection of the frequent early involvement of the cervical nodes in Hodgkin's disease.

The peak age incidence for non-Hodgkin lymphomas is in the sixth and seventh decades. Those in benign lymphoepithelial lesion are typically a complication of long-standing disease and are also therefore more likely to be seen in the elderly. Women are more frequently affected in the ratio of nearly 2:1. This is partly a reflection of lymphomatous change in Sjögren's syndrome. In such cases, symptoms of Sjögren's syndrome, sometimes of long duration, may be associated, or there can be features of another connective-tissue disease.

With regard to Hodgkin's disease, the juxtaglandular nodes, rather than the salivary glands are involved and there is a peak in the third and fourth decades. Males predominate in the ratio of 4:1.

A salivary gland lymphoma usually causes a firm swelling which in the majority of cases is painless. There is sometimes fixation to deep or superficial tissues and rarely (Gleeson et al, 1986a) facial palsy.

In 15 cases reported by Takahashi et al (1990) from Japan, 93% were in the parotid and the remainder in the submandibular glands; the mean age was 59 years and the male-to-female ratio was nearly 3:1. One patient had clinical evidence of Sjögren's syndrome.

Microscopy

Non-Hodgkin's lymphomas

The variety of classifications has made analysis of reports difficult. In the 59 cases reported by Colby and Dorfman (1979), salivary gland involvement in disseminated disease was included and all types of non-Hodgkin's lymphoma were represented.
In the 40 primary lymphomas reported by Gleeson et al (1986a), the single most common type was the follicular, predominantly small cleaved cell type, although there was little difference in frequency between follicular and diffuse types, and the majority were Grade I tumours. In the much larger series of 118 non-Hodgkin's lymphomas in salivary glands described by Seifert et al (1986) 90% were well differentiated (immunocytoma or centrocytic-centroblastic) and 10% were poorly differentiated (centroblastic or lymphoblastic).

The origin of salivary gland lymphomas has frequently been assumed to have been from MALT. To distinguish their site and cell origins, Kerrigan et al (1990) made use of specific gene rearrangements to provide a molecular marker. These are the immunoglobulin heavy-chain gene on chromosome 14 and \( bcl-2 \) gene on chromosome 18. A search was made for the t(14:18) translocation in extranodal lymphomas, but it was not found in any samples from the extranodal lymphomas of the stomach, intestine or skin, but was found in 3 of 7 salivary gland lymphomas, all of which were nodular. The remainder, lacking \( bcl-2 \) rearrangement were diffuse type and had histological or clinical features consistent with a MALT origin.

These preliminary findings therefore suggest that many salivary gland lymphomas are of MALT origin and that others which contain the \( bcl-2 \) rearrangement differ morphologically.

Hodgkin's disease

In most series including our own, primary manifestations of Hodgkin's disease in salivary glands are rare. However Schmid et al (1982) found four cases among 25 salivary gland lymphomas and (as mentioned earlier) Hodgkin's disease formed 15% of primary lymphomas in the series of Seifert et al (1986). In this latter series, 75% of the tumours were the result of disseminated disease so that 80% of the parotid tumours and 90% of the submandibular tumours were in lymph nodes only. The gland parenchyma was involved in only a minority and in none was the gland parenchyma alone involved. It appears therefore that the unusually high incidence of Hodgkin's disease in the material described by Seifert et al (1986) mainly results from inclusion of disseminated disease involving the cervical lymph nodes rather than Hodgkin's disease of salivary glands. Taking no account of whether these were primary or secondary lesions, there were virtually equal numbers of lymphocyte-predominant, nodular sclerosing or mixed type but only two were lymphocyte-depleted.

Prognosis and management

From the limited amount of published data it appears that salivary gland lymphomas are frequently well differentiated. However, as with lymphomas in other sites, the first essential is precise histological categorization followed by staging to determine whether the tumour is a primary salivary gland tumour or, if not, the extent of the disease.

If it can be established that the lymphoma is limited to a salivary gland, parotidectomy should be carried out and followed by radiotherapy. However, the treatment and prognosis will be determined by the stage and histological subtype and should be according to currently accepted protocols.
In the rare cases of Hodgkin's disease involving salivary glands, histological categorization is of even greater importance in determining whether radiotherapy or combination chemotherapy, or both, are most appropriate and should also be according to currently accepted protocols.

According to reports, such as those of Nime et al (1976) and Schmid et al (1982), the prognosis of primary salivary gland lymphomas appears to be better than that of nodal lymphomas. This is perhaps to be expected, in that a salivary gland lymphoma may be of relatively low grade and, in any case, is likely to be recognized at an earlier stage than a more deeply situated tumour.

**Lymphoma in Warthin's Tumour**

Lymphoma in Warthin's tumour is exceptionally rare. Rekers (1952) was probably one of the first to report a case. Colby and Dorfman (1979) noted lymphomatous stroma in 2 cases of Warthin's tumour, but it is not clear whether these represented lymphomatosus change in Warthin's tumour or involvement of the latter in disseminated disease. More recently, Bunker and Locker (1989) reported a case on which they carried out DNA analysis and in a review of the literature concluded that 12 other cases had been reported; of these 8 appeared to be primary lymphomas arising in Warthin's tumours. They also concluded that 11 cases had been previously reported but that 3 of these had not arisen primarily in the lymphoid stroma. Medieros et al (1990) have also reported a case and carried out immunophenotyping and gene rearrangement analysis on cryostat material. A typical Warthin's tumour was present but the majority of the stroma had been replaced by non-Hodgkin lymphoma which they categorized as being follicular and diffuse, of mixed small cleaved cell and large-cell type. Monotypic surface immunoglobulin could not be demonstrated but analysis showed rearrangement of both the immunoglobulin and kappa light-chain genes. The T-cell receptor beta-chain retained its germline configuration and confirmed the monoclonality and B-cell origin of the tumour.

The patient was a 71-year-old man who had had a mass at the angle of the jaw for five years but the growth of the mass had rapidly accelerated over the last two months. After partial parotidectomy the patient remained well four years later.

Clearly, it is impossible to make any useful statement about treatment of tumours as rare as these, but there seems to be no reason to suggest that they should be managed differently from other lymphomas of salivary glands.

**Juxtaglandular Tumours**

Tumours from adjacent tissues, other than lymph nodes, that involve salivary glands, or clinically appear to be salivary gland tumours are uncommon. The skin is probably the most frequent site of origin, but the cutaneous origin of such tumours is usually evident clinically.

Tumours of the mandible, such as an ameloblastoma, can also extend into the parotid but only very rarely. In any case mandibular tumours are uncommon and rarely extend outside the ramus.
Among the BSGTP material is a jugulotympanic paraganglioma which was initially mistaken for a clear cell acinic cell carcinoma of the parotid gland (Fig. 8.12). Its true nature was suggested by an astute surgeon who was impressed by its vascularity and the fact that it was fungating into the external auditory meatus. Paragangliomas stain in a generally similar manner to neuroendocrine cells but are negative for epithelial markers. Their cells are typically also in nests (Zellballen) and as the operative picture suggested, are more vascular than acinic cell carcinomas.

Tumours of the masseter muscles are exceedingly rare but a rhabdomyosarcoma can arise there and mimic a parotid tumour clinically.

Metastatic Tumours

Metastases to salivary glands are so uncommon that data on the relative frequency of the different types are conflicting. The most important in most respects, though not necessarily the most frequent, is a renal cell carcinoma, which as discussed earlier, must be distinguished from a clear-cell salivary gland tumour as has been well illustrated by Thackray and Lucas (1974).

In the BSGTP material there were only 19 metastatic tumours. Of these, 12 were in the parotid, six in the submandibular and one in the minor glands.

One difficulty is that secondary deposits in juxtaglandular parotid lymph nodes may extend into, and appear to have formed in, the gland, though from the viewpoint of management or prognosis, the distinction is unlikely to be of any significance. Despite the fact that adenocarcinomas are, overall, the most common malignant tumours in the body and might therefore be expected to be the most frequent type of metastasis in salivary glands, this does not seem to be the case. However, then a metastasis from a distant primary adenocarcinoma forms in a salivary gland, it may sometimes be difficult to distinguish it from a primary salivary gland tumour and it is possible that this problem may have distorted the reported data.

Conley and Arena (1963) have reported that the most frequent types of metastases from skin tumours, in salivary glands, were malignant melanomas (45%) and epidermoid carcinomas (37%) but these metastases were in parotid lymph nodes rather than the salivary gland. Pope and Lehmann (1967) have also stated that head and neck melanomas are the main source of metastases to parotid lymph nodes. Nevertheless, only a single case of metastatic malignant melanoma has been seen among 3500 salivary gland tumours in the BSGTP material and, in this case the primary tumour was in the eye. Ball and Thomas (1990) have reviewed previous cases and discussed their management.

Diagnosis and management

Diagnosis, obviously enough, depends on recognition of any feature that suggests that the tumour is a secondary deposit. This may be more easily said than done, unless the patient is known already to have a distant primary. It is reasonable to assume, for example, that a melanoma would be a secondary deposit, but as indicated earlier, this may not be the case, or alternatively, the tumour may be in some hidden carcinoma, the differential diagnosis from
a primary clear-cell carcinoma, has been discussed earlier (Chapter 7) but as indicated there, it is not always possible to make the distinction on the microscopic features alone. Ultimately, therefore, whenever a salivary gland tumour has microscopic features suggestive of a secondary deposit, confirmation of the diagnosis usually depends on investigation to confirm the presence of the primary tumour. This may be greatly facilitated by modern imaging techniques.

In the case of salivary gland metastases from distant sites, the prognosis is usually poor and palliative treatment is likely to be all that can be offered. In the case of metastases to the parotid glands, the diagnosis is usually made only after parotidectomy and, unless the tumour recurs in this site, no further treatment of this area is usually necessary or helpful. One exception may be the case of metastatic melanomas for which Ball and Thomas (1990) suggest that, though the long-term prognosis is poor, parotidectomy and elective neck dissection provide valuable loco-regional palliation. Another may be that of a renal cell carcinoma as discussed in Chapter 7.

In the case of spread to salivary glands of tumours from adjacent tissues (usually either from the skin into the parotid gland or from the oral mucosa to the submandibular gland), there is unlikely to be any problem of diagnosis. Moreover, the involvement of a salivary gland is usually evident clinically and removal of the primary tumour, and of the gland, may be manageable by a single wide resection, together with any lymph nodes that are involved. Nevertheless, the prognosis under these circumstances is also likely to be poor.

**Intraosseous Salivary Gland Tumours**

Salivary gland tissue is occasionally found within the body of the mandible. The usual site is near the angle of the jaw where an extension of the submandibular gland indents or may have become entrapped in the bone during development of the jaw. The defect is asymptomatic and only noticed by chance in a routine radiograph, as a sharply circumscribed, cyst-like area of radiolucency near the angle (Stafne bone cavity) or more rarely in the anterior part of the mandible (Chapter 3).

Rarely, salivary gland tumours develop within the jaw and presumably arise from these foci of ectopic tissue. Two trabecular adenomas, a few pleomorphic adenomas and adenoid cystic carcinomas have been reported in this site but most intraosseous salivary gland tumours have been mucoepidermoid carcinomas. Waldron et al (1987) reported 16 intraosseous mucoepidermoid carcinomas among 426 tumours of minor salivary glands. Waldron and Koh (1990) reported four more of these tumours and concluded that, so far, 66 central mucoepidermoid carcinomas had been reported. Hirota and Osaki (1989) reported a case of central adenoid cystic carcinoma in the mandible but were able to find reports of only seven other cases.

**Clinical and radiographic features**

The mandible is affected almost three times as frequently as the maxilla. Moreover, it is difficult to be certain that intraosseous maxillary tumours have not arisen in antral mucous glands rather than within the bone. In any case, unlike the mandible, there appears to be no ectopic salivary tissue within the maxillary bones from which these tumours could
arise. Of the 66 central mucoepidermoid carcinomas reviewed by Waldron and Koh (1990),
the age range was 1-85 years, with a mean age of approximately 50 years. Swelling of the
jaw was the main clinical feature in > 50% of cases and there was pain or paraesthesia in
30%.

The radiographic appearance of intraosseous salivary gland tumours is variable. They
may appear as uni- or multilocular rounded areas of radiolucency which, if benign or of low-
grade malignancy, appear well circumscribed and typically resemble odontogenic cysts. Their
nature is only recognized after a biopsy or excision has been carried out (Fig. 8.13 and 8.14).
High-grade tumours or central adenoid cystic carcinomas are likely to show some signs of
peripheral bone destruction and appear less sharply circumscribed.

**Microscopy**

Intraosseous salivary gland tumours do not differ microscopically from their soft-tissue
counterparts. It is important not to mistake them for one of the many types of odontogenic
tumours, but most of the reported intraosseous salivary tumours have been of readily
recognizable types.

**Management**

Once the histological diagnosis has been made it may be thought necessary to exclude
the possibility that the tumour is a secondary deposit by screening other organs. However, this
is extremely unlikely and all the cases reviewed by Waldron and Koh (1990) appear to have
been primary tumours. Adenocarcinomas of other organs can occasionally resemble salivary
gland tumours microscopically, so that metastases from other sites should be excluded (Fig.
8.15).

Most information is available about the results of treatment of central mucoepidermoid
carcinomas, but the numbers are so small and treatment options that have been adopted have
been so varied as to yield little useful information. However, in view of the unpredictable
behaviour of mucoepidermoid carcinomas, it seems that wide excision, or if necessary,
resection of the jaw and bone grafting, should be carried out. Some central mucoepidermoid
carcinomas appeared to have responded to simple enucleation but nearly 45% of those so
treated have recurred. As with mucoepidermoid carcinomas in salivary glands, the behaviour
is unpredictable and Lebsack *et al* (1990) have reported a central mucoepidermoid carcinoma
of the jaw that metastasized to a clavicle. The primary tumour was excised and radiotherapy
given to both the mandible and clavicle. They also reviewed seven previously reported cases
of metastases to lymph nodes, two of which were in adolescents. In the case of an adenoid
cystic carcinoma, spread along the inferior dental nerve may necessitate even wider excision.

Radiotherapy appears to be of uncertain value. For example, one of the patients
reported by Waldron and Koh (1990) died within nine months of initial surgery followed by
external-beam irradiation.

An intraosseous salivary gland adenoma if completely encapsulated, may shell out, as
in the case reported by Bret Day and Cawson (1969), and cause no further trouble.
Histogenesis

Though there may be doubt whether salivary gland tumours arise within the substance of the jaws, the fact that they do not arise from overlying minor salivary glands is shown by the absence of a soft-tissue mass, but central bone destruction with, initially, intact cortical plates. Though they are rare, the existence of benign intraosseous salivary gland tumours also indicates an origin within the bone. Credence is lent to this idea by the known presence of ectopic salivary tissue in Stafne bone cavities and in other parts of the jaws. Development of a pleomorphic adenoma has also been reported in a Stafne bone defect and presumably arose in an extension of the submandibular gland. Aberrant salivary tissue has not apparently been described in maxillary bone where salivary gland tumours are considerably less frequent and their central origin more difficult to confirm.

Waldron and Koh (1990) consider the possibility, among others, that a salivary gland tumour might arise from a glandular odontogenic cyst or from the mucous cells frequently seen in odontogenic cyst linings. Nevertheless, ectopic salivary tissue seems to be the most obvious source of neoplastic change, but the frequency with which this takes the form of mucoepidermoid carcinoma is puzzling.

Note

Preoperative Considerations

While all aspects of salivary gland surgery are covered in this chapter, in this section it is necessary to concentrate mainly on the parotid glands both because this is the most common site for tumours and also because it presents the greatest surgical difficulties and the greatest risk of cosmetic damage. Treatment planning for patients with salivary gland tumours is always difficult and, at least initially, arbitrary decisions have to be made for the following reasons.

First, it is impossible to predict behaviour without a conventional biopsy and for that matter, as discussed earlier, the behaviour of some of the rarer tumours is not yet known for certain. However, if it is available, preoperative fine-needle aspiration cytology, followed by frozen-section confirmation during operation, may be valuable in suggesting the need for more radical procedures which may involve sacrifice of the facial nerve and neck dissection. Nevertheless, in many cases, the diagnosis is only made postoperatively.

Second, it may be impossible to make anything more than an arbitrary decision as to the extent of the excision and, if function of the facial nerve is unimpaired, whether or not to sacrifice it. There is also considerable variation in the interpretation of what constitutes a parotidectomy. However, if excision does not appear to have been adequate, the need for reoperation or completion surgery has inevitably to be judged in each individual case from the operative description, the tumour type and its margins, as indicated by the histological findings.

Further, many salivary gland cancers are secondary or tertiary referrals following open biopsy, attempts at enucleation or superficial parotidectomy. In such cases the excision is likely to have to be even more extensive and involve removal of all the area of operation where tumour cells may have had a chance to seed and grow.

Third, there is the perennial problem of prophylactic neck dissection. On the one hand, micrometastases will be present in a significant number of patients, on the other is the inevitable morbidity of neck dissection in the absence of nodal involvement. We have therefore tried to indicate which tumours appear to have particularly low survival rates to allow the surgeon to decide, from experience, whether prophylactic neck dissection is justified.

A fourth consideration affecting management is that of the patient's age. Malignant tumours are significantly more frequent in elderly patients. There is often reluctance to operate on a patient over 80 years. This reluctance may be justified after clinical investigations and fine-needle aspiration biopsy have shown that the tumour is benign or of low-grade malignancy. In some of these cases the tumours appear to be progressing so slowly that the patient's expectation and quality of life may possibly be better if there is no operative
interference. However, this involves taking the risk that the tumour will maintain its behaviour pattern for sufficiently long, but this is always uncertain. By contrast, some patients may feel that to have to live with a tumour is unacceptable and their request for surgery should be respected. If this is agreed and the patient is fit for the operation, surgery should be definitive, not palliative.

Fifth, the role of radiotherapy has to be considered and has been discussed earlier, as best we can, in relation to individual tumour types. However, there is no firm evidence that radiotherapy is satisfactory as the primary treatment of any salivary gland tumours apart from lymphomas. Nevertheless, it may sometimes usefully supplement surgery, particularly for other malignant tumours.

High success rates have been claimed for neutron-beam (cyclotron) therapy, but the numbers of salivary gland tumours that have been treated have been so small and the period of follow-up so short, that results are of no statistical significance.

There is also no clear evidence as to the value of chemotherapy except perhaps as a treatment of last resort. More information is available on the effects of chemotherapy on oral cancers where Stell (1990) in a meta-analysis of published reports has shown that the mortality is actually increased by the toxic effects of the drugs. There is little to suggest, as yet, that chemotherapy of salivary gland cancer is likely to be any more useful than for oral cancers. Such evidence as there is, is no more than anecdotal in terms of numbers of patients and duration of follow-up.

In the management of salivary gland cancer therefore, it has to be accepted that no hard and fast guidelines can be drawn. Our aim has been to provide the best information available to us, but inevitably, it is not enough in a field where new types of cancer are being recognized faster than knowledge about their management.

In summary, the patient will fall into one of a number of clinical categories and the approach chosen will have to take into account these possibilities:

➤ New patients (primary referrals):
   - clinically benign tumours
   - clinically suspicious tumours (short history or pain)
   - clinically malignant tumours (facial or other cranial nerve palsy; or ulceration).

➤ Patients sent by other surgeons in the immediate postoperative period:
   - for further management of previously unsuspected malignancy;
   - for management of complications (mainly facial palsy);
   - after incomplete resection.

➤ Patients with recurrent disease.
With these problems in mind, each should be considered for the following treatment options, namely:

➤ Limited or radical resection (for example, superficial, total conservative or radical parotidectomy).

➤ Revision surgery.

➤ Complementary surgery (neck dissection, facial re-animation or exploration and nerve grafting).

➤ Radiotherapy.

➤ Chemotherapy.

**Surgery of the Parotid Gland**

Resections of the parotid gland are without doubt the most demanding form of salivary gland surgery because of the difficulty of avoiding damage to the facial nerve. As discussed later, the anatomy of the facial nerve within the gland is subject to variation and its identification may be further complicated by distortion of its course by tumours, scarring secondary to past inflammatory disease or surgery, or congenital abnormalities such as haemangioma or cystic hygroma. Inadvertent damage to the facial nerve may produce partial or complete facial palsy, either temporary or permanent. Apart from the obvious and immediate cosmetic disfigurement, eye problems, masticatory difficulties, gustatory sweating and subsequent synkinesis of facial expression, all contribute to the patient's continuing misery. While the risk of facial nerve damage can be minimized by experience and modern techniques, it cannot (and should not) always be avoided.

The literature is complicated by a multitude of terms that have been used to describe the various surgical procedures that have been undertaken on the parotid gland. Most confusion has arisen between the interpretation of the terms 'enucleation', 'limited excision' and 'superficial parotidectomy'. To most surgeons the term 'enucleation' implies the shelling out of a lesion, while to others it means the careful extracapsular dissection or even resection of the tumour together with a small cuff of apparently normal salivary tissue. Some consider an operation which defines the main trunk of the facial nerve before removal of the lesion together with a margin of normal tissue to be a superficial parotidectomy, while others reserve this term for the complete removal of all salivary tissue lateral to the facial nerve and would prefer the term 'limited excision'. It is very important to be clear about this terminology and be precise about the degree of parotid resection that has been undertaken particularly in the operative notes. Undoubtedly the differences that currently exist in the interpretation of the terminology have been responsible for persistent controversy about the best method of treatment for benign salivary tumours and also for reported differences in the recurrence rates following surgery. Besides this, it is essential to know exactly what was done at primary surgery when planning secondary procedures, for example for recurrent disease.
Fundamentally there are five commonly described operations on the parotid gland, which we define as follows:

1. **Enucleation.** Sometimes called an extracapsular dissection, is the removal of a parotid tumour by capsular dissection without reference to the facial nerve. This implies that there is a complete definable capsule, but as discussed in Chapter 6 this is frequently lacking.

2. **Limited excision.** The removal of a parotid tumour together with a wide cuff of normal tissue after finding and dissecting the main trunk and relevant branches of the facial nerve, but leaving some apparently normal parotid tissue lateral to the facial nerve.

3. **Superficial parotidectomy.** The removal of all, or at least most, parotid tissue lateral to the facial nerve.

4. **Total conservative parotidectomy.** The removal of all, or at least most, parotid tissue superficial and deep to the facial nerve with preservation of the nerve.

5. **Radical parotidectomy.** The removal of all parotid tissue together with the facial nerve. In the presence of a highly malignant tumour or evidence of extensive local spread this procedure may be combined with an *en bloc* neck dissection, resection of the mandibular ramus, maxillary tuberosity or petrosectomy.

Synchronous facial re-animation may be indicated in some cases where the facial nerve has been resected at its main trunk or major divisions. In others where resection of the major branches of the nerve has not been necessary, a more expectant approach should be adopted. Several months should pass to allow spontaneous recovery of neural function to be assessed before resorting to reconstructive surgery which might also include the transfer of tissue to fill out an operative defect. During this period it may be necessary to protect the eye with a temporary tarsorrhaphy.

**Guidelines**

The following guidelines are recommended but it cannot be pretended that there is any definitive protocol for any of the categories suggested earlier.

**Indications for enucleation**

None. Although a body of opinion suggests that certain lesions of the parotid gland can be treated or investigated in this fashion, for example, lymphoma, it is the authors' opinion that this is bad and unsafe practice and should not be encouraged.
**Indications for limited excision**

➤ As primary treatment for benign tumours arising in the lower pole of the parotid gland.

➤ In some cases of recurrent disease where there has been adequate primary surgery and the recurrence is distant from the majority of branches of the facial nerve. In these cases aggressive dissection of the nerve is likely to lead to an unacceptable neural deficit.

**Indications for superficial parotidectomy**

➤ As primary treatment for benign or malignant salivary tumours situated totally lateral to the facial nerve and not involving it.

➤ For secondary referrals following incomplete excision of benign tumours, which may recur, superficial to the facial nerve.

➤ In conjunction with a radical neck dissection for the control of squamous-cell carcinoma arising on, or around, the face in order to remove first echelon nodes.

**Indications for total conservative parotidectomy**

➤ Resection of benign salivary tumours occupying both deep and superficial lobes of the parotid gland (dumb-bell tumours) and low-grade malignant tumours not involving the facial nerve.

➤ Control of recurrent sialadenitis.

➤ For recurrent benign tumours, but only when the facial nerve is readily identifiable.

➤ To remove parapharyngeal tumours.

**Indications for radical parotidectomy**

Resection of malignant salivary or adnexal tumours involving, or in such close proximity to the facial nerve that it cannot be dissected clear of the tumour without jeopardizing the surgical margins.

**Contraindications to parotid gland surgery**

Poor general health is the only valid contraindication to surgery on this gland. In general, it is tolerated well by the patient, the only proviso being their fitness for general anaesthesia.
Preoperative Investigations

Imaging

Computerized tomography and MRI do not contribute surgically significant information about the majority of suspected parotid neoplasms, but specific indications have been discussed in Chapter 2. Most may be resected quite safely after careful local and general clinical examination. Parotid masses which require detailed computerized tomography or MR imaging can be recognized on strictly clinical grounds, namely:

➤ All masses with suspected deep-lobe involvement or that are displacing the soft palate and superior pole of the tonsil medially.

➤ All tumours causing any degree of facial weakness or known to be malignant.

➤ Extensive lesions or those with suspected local or regional spread.

➤ All recurrent tumours.

It is a *sine qua non* that all patients with suspected neoplastic disease should also have a chest radiograph. Although uncommon, the presence of unsuspected pulmonary metastases greatly influences patient management.

Biopsy

Open biopsy is absolutely contraindicated and the role of fine-needle aspiration cytology is considered by some clinicians to be controversial as discussed earlier. However, there is no doubt that in expert hands FNAC can sometimes convey to both the surgeon and patient several advantages. First, it is capable of warning the surgeon of malignant disease which may not have been suspected and which might necessitate facial-nerve resection. Second, lymphoma, infections and cysts should be readily recognized, thereby indicating further investigation before deciding on the role and extent of surgical intervention. Third, it is quick and simple to perform in the clinic and acceptable to the patient. Expertise in interpretation of fine-needle aspirates cannot develop without frequent practice and therefore it is the authors' opinion that it should be considered in every case. The risk of seeding in the needle track is very small indeed and has been discussed in Chapter 2.

Informed Consent

The patient should be gently but fully forewarned of the following possible complications.

Facial weakness

The risk of temporary or permanent facial weakness must be carefully explained. Facial nerve neuropraxia usually recovers within 4-6 weeks, but in severe cases is almost always associated with some degree of neural degeneration. Complete recovery of facial
symmetry may therefore take 6-12 months and in a few is never achieved. It is worth explaining to the patient that the risk of facial weakness applies equally to benign as malignant tumours because of the variable anatomy of the facial nerve and position of tumour relative to it.

**Facial anaesthesia**

Anaesthesia in the distribution of the greater auricular nerve (over the angle of the mandible and inferior two-thirds of the pinna) is unavoidable. It can be most irritating for the patient especially if not forewarned. No recovery should be expected as the greater auricular nerve is deliberately sacrificed during the resection. Most patients learn to accept this deficit with time.

**Cosmetic defects**

The patient may be reassured that the cosmetic appearance of the incision rarely causes concern. However, the loss of bulk behind the ramus of the mandible may result in a mildly unsightly dent in the normal outline of the jaw and make cleaning difficult. Bulk defects can be minimized by soft-tissue rotation flaps derived from the sternomastoid muscle.

**Frey's syndrome**

Gustatory sweating (Frey's syndrome) is a socially embarrassing complication of parotidectomy and develops in nearly all patients to some degree. Its frequency is sufficient to warrant preoperative explanation together with the reassurance that it is rarely significantly disconcerting and usually amenable to simple preventive measures, for example, the application of an antiperspirant (Chapter 5).

**Surgical Anatomy of the Parotid Gland and Facial Nerve**

The gross relationships of the gland have already been described in Chapter 1. From the surgical standpoint the most important and difficult aspect of parotid surgery has always been the management and location of the facial nerve. Surgeons undertaking parotidectomy during the first half of this century were severely hampered by what would nowadays be considered primitive anaesthetic techniques. Blood pressure was poorly controlled and diathermy dangerous in the presence of explosive anaesthetic agents. These two factors made haemostasis almost impossible and as a result, visibility of fine structures was very poor. Also, at that time, few were technically able to locate the main trunk of the facial nerve at the base of the skull. For the majority, therefore, reliable isolation of its divisions and branches was an impossible task. Indeed, they were not helped by the classical anatomical descriptions of the major salivary glands. These descriptions had been based on cadaver dissections and were in many respects inaccurate. While useful for surface markings and gross relationships, these descriptions failed to take into account the normal variations or describe detail relevant to the surgeon and essential for removal of diseased glands with minimal morbidity. As a result, potentially curable tumours were inadequately resected merely to minimize facial-nerve damage. Local excision, intracapsular removal, enucleation, with or without subsequent radiation, were widely practised and, sadly, are still practised and even advocated by some today. Consequently, various surgeons from all over the world have
reported recurrence rates of 10-50% with these techniques.

Familiarity with the form, location and peripheral distribution of the facial nerve is of paramount importance in salivary gland surgery. Studies over the past 30 years have helped to elucidate its detail and develop methods for finding it at a variety of peripheral sites. The following section is a synopsis of our current understanding of the extratemporal facial nerve as it applies to the parotid and submandibular salivary glands.

**Branching patterns of the extratemporal facial nerve**

In the vast majority of cases, the facial nerve leaves the skull as a single trunk through the stylomastoid foramen then splits within the substance of the parotid gland into zygomaticotemporal and cervico-mandibular divisions. The terms 'zygomaticofacial' and 'cervicofacial' respectively, are sometimes used for these divisions. Each division further subdivides to produce five major branches: temporal, zygomatic, buccal, mandibular and cervical. Katz and Catalano (1987) in a study of the facial nerve's anatomy in 100 patients undergoing parotidectomy, observed double trunked nerves in three individuals and cautioned surgeons that unless they were aware of this anomaly, unnecessary damage to the facial nerve could result. Others, in equally large or larger series, have failed to encounter this variant. However, detailed studies of the intratemporal course of the facial nerve have demonstrated both bifurcation and trifurcation of the main trunk within its mastoid segment and therefore the double-trunked, extratemporal, facial nerve must exist, though perhaps less frequently than Katz and Catalano suggested. Division of the facial nerve within the temporal bone is frequently associated with congenital abnormalities of the pinna or inner ear. An abnormally formed ear or congenital hearing loss should therefore alert the surgeon to this possibility. When present, the minor trunk of the facial nerve is said to enter the zygomaticotemporal division of the main trunk.

The pattern of branching of the facial nerve within the parotid gland is also variable. Although not the first to study the detailed ramifications of the nerve in cadavers, Davis et al (1977) were probably the most thorough. They performed dissections on 350 cervicofacial halves and classified the branching patterns of the facial nerve into six types. Miehlke et al (1979) studied the operation records of 100 patients at their institute and grouped the branching patterns into eight types. The more recent study of Katz and Catalano (1987) reclassified these patterns into only five types. This study has the advantage that it was derived from contemporary operative findings rather than cadaver dissections and, as a result, incorporated functional information and the postoperative significance of damage to some of the fine branches. This classification has therefore been adopted here as being the simplest and most practical.

The five types of branching patterns of the facial nerve are illustrated in Fig. 9.1 to 9.9 and are as follows:

**Type 1:** This pattern lacks anastomotic links between the main branches of each division. However, in one subtype, there is splitting and subsequent reunion of the zygomatic branch while in the other, the mandibular branch splits and reunites (Figs 9.1-9.2). Comprises 25%.
Type 2: In this type, subdivisions of the buccal branch fuse peripherally with the zygomatic branch (Fig. 9.3). Comprises 14%.

Type 3: There are major communications between the buccal branch and others (Figs 9.4-9.6). Comprises 44%.

Type 4: In this type there is a complex branching and anastomotic pattern between the major divisions (Figs 9.7-9.8). Comprises 14%.

Type 5: The facial nerve leaves the skull as more than one trunk (Fig. 9.9). Comprises 3%.

Unfortunately, it is impossible to incorporate the findings of other series into this classification, or indeed into any other, however detailed, that can be devised. This is not because of any doubt about the validity of the findings of the different workers in this field; the problems of producing a coherent picture of these anatomical details stem from the following:

➤ Some studies have been on cadavers and this has made it possible to extend dissections further than at operation. Some of these studies also have the advantage of having been made on very many specimens.

➤ Other studies have been peroperative, and though on smaller numbers of patients are of greater surgical significance in that it was possible to validate the findings by nerve stimulation.

➤ As mentioned earlier, the terminology of different authors varies.

An almost bewildering of patterns of branching of the facial nerve have thus been described and also, apparently, substantial differences in the frequency of the types of pattern have been found by different investigators. For example, Katz and Catalano (1987) found the Type 1 arrangement in 24% of their parotidectomies while Davis et al (1956) documented this straight branching pattern in 13% of their dissections. This difference may have been offset by another 20% of the series of Davis et al which were found to have complex zygomatic branches and might therefore have been considered to be Type 1 by Katz and Catalano (1987). In sharp contrast, Miehlke (1979) reported these patterns in 75% of his series.

Differences are even more apparent when considering the frequency of distribution of the other types. Katz and Catalano (1987) found the relatively simple anastomotic patterns, Types 2 and 3, in over 50% of their series and the more complex branching arrangement in only 10%. Similarly Miehlke, whose data were also based on operative records, found complex branching patterns in relatively few patients (5%). By contrast, Davis et al (1956) reported a much higher incidence of complex branching patterns (39%). It would seem that these apparent discrepancies between the relative frequencies of the types most probably reflects the ability of Davis et al (1956) to dissect further distally in the cadaver than either Katz or Miehlke needed to at operation.
Example may also be given of the confusion that is caused by the terminology different authors have used. A nerve that one author might describe as a 'division of the mandibular branch' is termed the 'cervical branch' by another. Nowhere is this more evident than in the distinctions between the zygomatic and buccal branches. Davis et al (1956) accurately noted that the zygomatic branch followed the parotid duct throughout the substance of the gland and was usually superior to it. Yet others, including the classical anatomical texts and dissections, state that the parotid duct is intimately related to the buccal branch. Some have gone so far as to recommend location of the buccal branch by exploring the course of the duct, which runs along a line drawn from the ear lobe to the vermilion border of the upper lip.

It is not surprising therefore, that a variety of terms for some of these branches has come into use in surgical parlance. For example, the complex branched patterns, just described, near the periphery of the facial nerve, and present in many patients, are referred to by most surgeons as 'vertical anastomoses'. The latter are important because there are two clinical circumstances in which their presence is of surgical significance. First, these anastomoses explain the unexpected absence of facial weakness when relatively major branches have been sacrificed or inadvertently damaged. Second, when undertaking selective denervation procedures such as for the treatment of blepharospasm, it is important to establish peroperatively that avulsion of the nerve branch has been achieved at an adequately peripheral site.

In summary therefore, there seems to be no doubt that many variations in the branching patterns of the facial nerve exist and the positions of these branches vary. However, the nature of any given pattern in a particular patient is quite unpredictable preoperatively and it is clearly impossible to take account of all possible patterns during parotid surgery. The most important consideration, therefore, is to be aware that many possible variations exist and to define the facial nerve and its branches as precisely as possible to taking into account its most frequently found patterns. The other consideration is that however much care is taken in seeking out the branches of the facial nerve, some damage to one or more of these branches may be unavoidable but is not necessarily catastrophic. Nevertheless, the existence of this multiplicity of variations makes it imperative to warn the patient of the possibility of some degree of functional deficit.

**Location of the facial nerve trunk and its branches**

In practice, there are three major difficulties in the management of the facial nerve in parotid gland tumours. The first, as discussed below, is the difficulty of preserving the major trunk and as many minor divisions as possible when dealing with a benign tumour. The second is to decide when to sacrifice the facial nerve when removing a malignant tumour. The third is to advise the patient of the possibility of either unavoidable damage if the anatomy proves to be abnormal or else of the need to sacrifice the nerve to allow complete removal of the tumour. These last two aspects are considered in relation to the section on total parotidectomy.

The methods of locating the facial nerve and its branches at operation are discussed later in this chapter. However, it may be useful to summarize the main points here, if only to emphasize the difficulties of defining reliable anatomical landmarks.
Identification of the facial nerve trunk is best achieved by reference to its immediate anatomical relations. A facial nerve monitor is particularly useful at this point in the operation, provided that the patient has not been paralysed by a muscle relaxant. The landmarks most commonly used are:

➤ The inferior portion of the cartilaginous canal. This is termed the ‘pointer’ and the facial nerve lies 1 cm deep and inferior to its tip.

➤ The groove between the cartilaginous and bony external auditory meatus. The sharp lateral edge of the tympanic ring at the antero-inferior border of the external auditory canal (the vaginal process) lies immediately superficial and superior to the nerve at its point of exit from the skull. This edge is easy to feel.

➤ The anterior border of the posterior belly of the digastric muscle. The facial nerve leaves the skull immediately anterior to the attachment of this muscle. Definition of the digastric muscle therefore outlines an area immediately anterior to it in which the facial nerve will be found.

Despite the use of these landmarks, repeated electrical stimulation is sometimes necessary to help to discriminate between stretched fibrous tissue and nerve. With continuous intraoperative monitoring, surgically evoked myogenic activity can be heard and acts as a warning that the nerve is being irritated by surgical manipulation or distortion.

Dissection of the facial nerve along a peripheral branch both centrally and distally was one of the first techniques to be developed and has proved to be one of the most useful. Recognition of the mandibular branch at the angle of the mandible, as it lies superficial to the facial vessels, is a pivotal surgical landmark today. Retrograde dissection of this branch to the main trunk is an important first step. A similar technique can be used to identify the cervical branch of the nerve at the point at which it pierces the deep fascia, below the body of the mandible.

Current surgical teaching to avoid accidental section of the mandibular branch, is to place the incision in a skin crease at least two finger breadths beneath the lower border of the mandible. However, the facial artery is a valuable palpable marker and the mandibular branch lies above the lower border of the mandible, posterior to the artery, in 81% of cases. Anterior to the artery, all mandibular branches are above the mandible (Fig. 9.10).

Nelson and Gingrass (1979) have questioned the reliability of the relationship of the mandibular branch to the lower border of the jaw. They isolated the rami supplying the labial depressors and found at least three branches in every case. The most inferior supplied the mentalis muscle and invariably ran entirely below the mandible. The branch to the depressor labii inferioris lay just above it and below the branch to the depressor anguli oris. This was the only branch found to run reliably at, or above, the inferior border of the mandible anterior to the facial artery. These nerves all ran deep to the platysma in the thin fascial layer overlying the submandibular gland. The surgical significance of these studies is that identification and preservation of one branch may not guarantee against subsequent weakness of the lower lip.
Bernstein and Nelson (1984) when examining the zygomaticotemporal division, found that four rami of the temporal branch crossed the zygomatic arch. All were anterior to the superficial temporal artery and evenly distributed over the articular eminence of the zygomatic process or middle third of the zygomatic arch. The frontal and orbital rami of the temporal branch ran consistently to the lateral edge of the eyebrow at the frontozygomatic suture within a strictly defined area (Fig. 9.10). This area was bounded by a line from the ear lobe to the lateral edge of the eyebrow inferiorly and superiorly by a second line from the tragus to the lateral coronal suture just above and behind the highest forehead crease. This suggests that incisions in this part of the face should be made superior and posterior to the temporal vessels and that identification of the superficial temporal artery at the upper pole of the parotid followed by soft-tissue dissection towards the lateral edge of the eyebrow should expose the temporal branch and its rami.

Bernstein and Nelson (1984) also described tethering of the temporal and zygomatic branches by anastomotic rami from the auriculotemporal nerve and the relationship of these rami to the superficial temporal and transverse facial arteries and veins. The facial nerve branches may embrace the transverse facial vessels and should therefore be approached with extra care at this point (Fig. 9.11).

The intimate relationship of the parotid duct and zygomatic branch of the facial nerve has been noted by many. The duct runs along a line drawn from the tragus to the vermilion border near the angle of the mouth and enters the mouth opposite the upper first molar tooth, 0.5-1.0 cm anterior to the masseter muscle. It lies inferior to the zygomatic branch, though is frequently overlain by numerous zygomatic rami.

The anatomical relations of the main trunk of the facial nerve at the stylomastoid foramen are described in the section on superficial parotidectomy (p. 203). In summary, a variety of landmarks for identification of the facial nerve and its branches have been described and it is important to emphasize that a combination of these landmarks usually needs to be used.

The deep and superficial lobes

The controversy surrounding the existence of an isthmus has been discussed in Chapter 1. The reason is that there has been a desire to establish why development of a surgical plane round the facial nerve within the parotid gland is relatively simple. It is now established that the facial nerve becomes engulfed by embryonic glandular parenchyma between the 16th and 21st week of fetal life. As the gland wraps itself around the nerve, a layer of loose connective tissue remains around it. This tissue forms the plane of dissection around the nerve and can be opened with ease during parotidectomy unless it has been destroyed by either recurrent infection or tumour infiltration.

It also seems likely that the presence and site of an isthmus might determine the origin and management of deep-lobe tumours. The presence of an isthmus between the major divisions of the facial nerve would also provide a route by which a tumour arising in the deep lobe can extend into the superficial lobe to form a dumb-bell shape. However, some large tumours arising from the deep lobe remain totally confined to the parapharyngeal space. It is possible that some of these may have developed from minor salivary gland tissue but if this
were the case they would be attached to the pharyngeal mucosa. However, this is rarely the case.

Some surgeons who believe that deep-lobe tumours arise from minor pharyngeal salivary glands manage them by either the transmandibular or transcervical approach. In effect, they are performing an enucleation and do not remove the whole parotid gland. This approach has disadvantages which are discussed later not the least of which is the very significant risk to the facial nerve.

It is also known that the deep lobe drains by a separate system which joins the main excretory duct. However, the precise position of the isthmus is probably variable.

**Surgical anatomy of the autonomic nerve supply**

The secretomotor fibres to the parotid gland emerge from the otic ganglion which is closely related to the auriculotemporal nerve. Preganglionic fibres reach the ganglion from the inferior salivary nucleus via the glossopharyngeal nerve, tympanic plexus and lesser superficial petrosal nerve.

Surgeons have attempted to interrupt this pathway in an attempt to alleviate severe Frey's syndrome. The most accessible approach to the parasympathetic pathway is in the middle ear, where the tympanic plexus can be destroyed on the promontory. Others have attempted to avoid this complication by avulsing the auriculotemporal nerve during parotidectomy or even by interposing a fascial graft, or muscle flap, between the cut surface of the gland and the skin flap to prevent subsequent regrowth of postganglionic secretomotor fibres into the sweat glands of the skin. As discussed earlier, neither of these measures gives predictable results nor long-standing relief.

The sympathetic supply reaches the gland from the superior cervical ganglion via the neural plexus surrounding the major blood vessels. The effects of drugs acting on these autonomic pathways has been discussed in more detail in Chapter 5.

**Superficial Parotidectomy. Operative Procedure.**

**Preparation**

After skin preparation and towelling, it is helpful to infiltrate the superficial tissues with 1:200,000 adrenaline solution. This aids the development of the skin flaps and improves visibility around the facial nerve at the most critical stage of the operation.

**Incision**

Most surgeons use the 'lazy S' incision with appropriate extension into the hairline or neck for larger tumours (Figs 9.12 and 9.13). In the past, a variety of incisions has been described, all of these aimed to gain maximal access to the retromandibular fossa and parotid gland, while at the same time being cosmetically acceptable (Fig. 9.14). Occasionally, these are still useful but each has disadvantages of which the surgeon should be aware. A purely retroauricular incision, although cosmetically attractive, fails to give adequate space and
visibility anteriorly and superiorly. The rhytidectomy incision favoured by some plastic surgeons has the same limitations. Superior displacement of the pinna with a 'Y' incision provides maximal exposure of the main trunk of the facial nerve which can be access in the temporal bone, but for total conservative parotidectomy, the extra access afforded over the 'lazy S' incision is seldom required. In addition, the resultant three-point junction with its attendant problems of diminished tissue viability is a distinct disadvantage. The preauricular incision as described by Blair (1941), with extension onto the zygoma, affords good access but is cosmetically unsatisfactory. The 'lazy S' incision was developed from the incision first described by Bailey (1941). He advocated the preauricular component linked to a skin-crease incision in the neck by a pronounced retroauricular extension. The extension behind the ear had a most precarious blood supply, did not improve cosmesis and was found to be unnecessary.

Skin flaps should be raised with considerable care as cutting too thin can easily result in button-holing, but if too thick, endangers the facial nerve anteriorly. The correct level is just above the parotid fascia, well below that of the hair follicles, which if seen, indicate that the flap is too thin. The skin flap should be raised as far anteriorly as the posterior border of the masseter muscle and posteriorly sufficiently far to allow complete access to the parotid gland. The raised flaps are sutured to the towels and covered with saline-moistened swabs (Figs 9.15 and 9.16).

**Mobilization of the gland**

The second part of the dissection aims to free the posterior margins of the gland to allow the facial nerve to be safely identified at a point just distal to its exit from the stylomastoid foramen. Dissection should start at the anterior border of the sternomastoid muscle and necessitates transection of the greater auricular nerve and sometimes, ligation of tributaries of the external jugular vein. The gland is gradually mobilized by both blunt and sharp dissection towards the mastoid process and around the cartilaginous external auditory canal to a point superior to the tragus. The tissue plane between the parotid gland and these structures is relatively easy to define. The subsequent dissection is considerably simplified if the operator stays strictly within this layer.

**Location of the facial nerve**

Identification of the facial nerve can be very difficult, especially if the gland is not or cannot be well mobilized, and requires both experience and patience. It is best achieved by reference to several structures which are its immediate anatomical relations. A facial nerve monitor is particularly useful at this point in the operation, but if this is not available, the surgeon should have a variable output nerve stimulator. Neither can work if the patient is paralysed and therefore the anaesthetist should check that the action of any short-term muscle relaxant has been totally reversed. The landmarks most commonly used are (Figs 9.17 and 9.18):

➤ The inferior portions of the cartilaginous canal. This is termed the 'pointer' as it indicates the position of the facial nerve which lies 1 cm deep and inferior to its tip.
The groove between the cartilaginous and bony external auditory meatus. The sharp lateral edge of the tympanic ring at the anterior-inferior border of the external auditory canal (the vaginal process) is easy to feel. It lies immediately superficial and superior to the nerve at its point of exit from the skull.

The anterior border of the posterior belly of the digastric muscle. The facial nerve leaves the skull immediately anterior to the attachment of this muscle. Definition of the digastric muscle therefore serves two purposes. First, it mobilizes the parotid gland and second, it outlines an area immediately anterior to it, in which the facial nerve will be found.

Location of the facial nerve by this method may be hindered by the tumour itself which can lie over the nerve or behind it, thereby displacing it laterally into an unexpected position. During this phase of the operation, the assistant plays an equally important role in providing adequate retraction for maximal vision, without either rupturing the tumour mass or inadvertently damaging the nerve by pressure. In a high proportion of cases, and with experience, the nerve is found easily but in some cases the surgeon must gently separate each strand of tissue in the zone until the nerve is reached. This is most easily undertaken with a peanut swab and small, blunt, dissecting scissors. Repeated electrical stimulation will help to discriminate between stretched fibrous tissue and nerve, though this should never be accepted as definitive proof if the surgeon is in doubt. If doubt remains the surgeon should work from a different angle in order to define the structure more clearly. Control of haemorrhage is vital as bleeding, no matter how minor, considerably handicaps the visibility of the surgeon. Forceps, clips and bipolar diathermy must be used with extreme caution as the nerve is approached. The stylomastoid artery which lies immediately lateral to the nerve at the skull base is particularly troublesome in this respect. If torn, it bleeds briskly and this should be an additional warning of the proximity of the nerve. Even bipolar diathermy is dangerous at this juncture and should bleeding be a problem, swabs soaked in adrenaline 1:200,000, can be usefully applied to staunch the ooze.

**Dissection of the facial nerve**

Once found, the trunk of the nerve is exposed further by firmly inserting a pair of fine artery clips or scissors into the perineural plane, spreading them to create a tunnel and then incising the overlying parotid tissue with a No. 12 blade (Figs 9.19 and 9.20). The major divisions and branches of the facial nerve are then followed to the periphery in this manner, beginning with the upper division and progressing inferiorly. In this way, the superficial lobe and tumour are peeled off the facial nerve. The upper division of the nerve, unlike the inferior, tends to be slightly tortuous and can be inadvertently damaged unless great case is taken when opening the tunnels created by perineural dissection. The parotid duct is sometimes encountered running parallel and inferior to the zygomatic branch of the facial nerve and may restrict mobilization at the anterior part of the dissection unless transected and ligated.

It may not be necessary to dissect the nerve completely as a perfectly adequate tumour clearance may be achieved with a more conservative or near total resection of the superficial lobe. The precise amount of parotid tissue that should be removed depends entirely on the size of the tumour and its location. Occasionally, it is also necessary to remove part of the
deep lobe to obtain a satisfactory margin.

Branches of the facial nerve *inseparably adherent* to tumour, or running through it, must be resected. If the resected segment is either the upper or lower division it should be repaired immediately with a cable graft. Donor segments can be harvested from the greater auricular nerve, if this is not involved by tumour or the sural nerve. The result of damage immediately peripheral to the major divisions is sometimes considerably less than would be expected. Compensatory innervation from adjacent branches, through the vertical system of anastomoses, would seem to account for this fortunate phenomenon.

**Closure**

Vacuum drainage should be inserted and the wound closed in two layers with Vicryl or chromic catgut subcutaneously and monofilament nylon for the skin. Drainage is maintained until < 25 mL has escaped during a 24-hour period and the sutures are removed after 7 days.

**Total Conservative Parotidectomy Operative Procedure**

**Incision**

Extension of a 'lazy S' incision into both the hair-line and neck is a prerequisite for this procedure if undertaken for the removal of a tumour. However, many cases of chronic sialadenitis can be managed quite satisfactorily without this additional access. The only other distinction in technique is that removal of the deep lobe should be in continuity with the superficial lobe in tumour surgery. A more piecemeal approach to the deep lobe can be taken in patients with intractable sialadenitis. The first part of the operation is identical to that of superficial parotidectomy.

**Exposure of the facial nerve**

The facial nerve is identified and the superficial lobe of the gland reflected inferiorly so that the deep lobe remains connected to it only by glandular tissue inferior to the mandibular branch. The main trunk of the nerve and its divisions are then gently freed from the lateral aspect of the deep lobe (Figs 9.21 and 9.22). This is a very delicate procedure which requires great care on the part of the surgeon and assistant. At this stage, the minimum of tension and traction should be applied to the nerve. It is best elevated by steadying the adjacent salivary tissue with a small swab and carefully dissecting beneath a segment of the nerve with curved Kilner scissors. Once this has been separated, a nerve hook, plastic sling or the gentle curve of a fine artery clip provides safe elevation and gentle traction. From this vantage point, dissection can proceed both peripherally to the posterior margin of the masseter and centrally to the stylomastoid foramen. Continuous attention must be paid to the position and tension applied to the nerve when free from the deep lobe, as it can be easily overlooked while manoeuvring a deep lobe tumour and unnecessarily damaged.

Before removing a tumour, the external carotid artery, at the inferior pole of the gland, together with its terminal branches - the maxillary, superficial temporal and transverse facial arteries - at the superior and anterior margins, should be ligated (Figs 9.23 and 9.24). The
veins related to the latter arteries must also be tied. This is not necessary in cases of chronic inflammatory disease for which piecemeal clearance of the residual gland, between the branches of the facial nerve, is perfectly acceptable.

Dissection of the deep lobe

Once free from the nerve, the deep lobe and tumour, if large, are gradually mobilized by finger dissection (Figs. 9.25 and 9.26). However, if the deep extension is small, dissection with forceps and scissors is more appropriate and certainly less traumatic to the nerve. With care, the tumour can be released from its attachments to the lateral pharyngeal wall and cranial base. Small and soft tumours of the deep lobe may be manipulated beneath the mandibular branch of the facial nerve and removed in continuity with the superficial lobe. This process is facilitated by the assistant's finger, placed in the patient's mouth, exerting gentle lateral pressure on the tumour.

Unfortunately, many tumours in this site are large and become trapped between the styloid process, ramus of the mandible, stylomandibular ligament and base of the skull. Additional space is required to manipulate them free without damaging the facial nerve. For most, division of the digastric muscle and stylomandibular ligament is sufficient, but a few may need temporary, anterior dislocation of the mandible, osteotomy or even partial resection of the ramus.

Several different access osteotomies of the mandibular ramus have been described (Fig. 9.27). Some are technically easy while others are more demanding. From the patient's standpoint, time and care spent performing the more complicated procedures is rewarded by minimal morbidity in terms of mandibular nerve deficits and subsequent bony union. For these reasons, an angle osteotomy is no longer acceptable and the L-shaped osteotomy of the ascending ramus described by Trauner and Obwegeser (1957) is most appropriate. There are two critical measurements in this technique which relate to the position of the linguula on the medial aspect of the ramus and therefore help the surgeon avoid inadvertent damage to the mandibular nerve. It lies 15 mm anterior to the posterior margin of the ramus and 45 mm above the lower border of the mandible. The outline of the vertical osteotomy should be marked on the surface of the mandible which has been appropriately stripped of the attached masseter muscle fibres. Mini-plates are prepared and fitted so that the bone can be reconstructed precisely after resection of the tumour as described later (p. 209-10). By dissecting between the masseter and the ramus, and retracting the masseter laterally, the anterior border of the mandible is identified and the position for the horizontal limb of the osteotomy can be defined. Section of the bone can be most accurately undertaken with a small oscillating saw. If such a saw is not available, the surgeon can make a series of pilot holes with a rose-head bur and subsequently connect them with a fissure bur, thereby completing the osteotomy. Some mobilization or relieving incision in the medial pterygoid muscle will be necessary to allow the mandibular segment to swing laterally. Such incisions should be kept to a minimum otherwise avascular necrosis of the mobilized segment may ensue.

Closure

Either vacuum, corrugated or tube drains should be inserted and the wound closed in two layers. The surgeon must be careful with vacuum drains that segments of the unsupported
nerve are not entrapped in the suction holes (Figs 9.28 and 9.29). It is for this reason that the author prefers corrugated drains in combination with a light pressure dressing to the side of the neck. Drains should be removed when the surrounding dressings remain dry, usually within the first 24-48 hours and the sutures after seven days.

Other Approaches to Deep-Lobe Tumours

Cervical and transoral approaches to the parapharyngeal space have been described. However, they are totally unsuitable for the management of deep-lobe parotid tumours because of the limited access that they provide. The only alternative to the transparotid technique is the transpharyngeal (jaw splitting or mandibular swing) approach.

Transpharyngeal Approach

Preparation

This approach is most appropriately used for large extraparotid parapharyngeal masses, namely those arising from minor oropharyngeal glands. It is particularly useful for vascular tumours such as extensive paragangliomas of the carotid body that encroach on the skull base, as it gives exceptionally good exposure. The cooperation of an oral surgeon is essential if the operator is inexperienced in mandibular fixation. Oral surgeons usually appreciate a few days' warning before surgery so that the dentition can be prepared, if necessary, for intermaxillary fixation by interdental wiring or cap splints. If the patient is edentulous Gunning-type splints might be required. However, the majority of cases are suitable for compression-plate fixation of the mandible for which little preparation is necessary and subsequent intermaxillary fixation is unnecessary.

After induction of anaesthesia a preliminary tracheostomy is performed to protect the airway, as this approach includes a mandibulotomy and, sometimes, subsequent intermaxillary fixation. The tracheostomy has the additional advantage of removing the endotracheal tube from the operative field and therefore increases the available exposure.

Incision and exposure

A skin-crease incision is made at the level of the hyoid bone and extended forwards around the chin to split the centre of the lower lip (Fig. 9.30). The contents of the carotid sheath are identified and traced to the base of the skull. The common and internal carotid arteries are secured with slings to enable rapid control of these vessels in the event of inadvertent rupture later on in the procedure. Often it is advisable to ligate the external carotid artery at this stage. The dissection is then continued deep to the submandibular gland until it is free from the surface of the hyoglossus muscle. Attention is then focused on the buccal gingivae which are very carefully elevated from the underlying bone over the chin. Holes are prepared on either side of the proposed, stepped, osteotomy and compression plates fitted. It is essential that the placement of the compression screws avoids the roots of the underlying incisor and canine teeth and that the plates are accurately bent to the outline of the mandible. Once fitted, the plates and their screws are removed and placed to one side until the end of the operation. A midline mandibulotomy is then made with a fine oscillating saw. If the lower incisors are overlapping or imbricated, it may be necessary to extract one of them to make
space for the bone cut. The mandible is then retracted laterally so that the incision can be extended between the papillae of the submandibular ducts, along the floor of the mouth and up the anterior faucial pillar to the superior pole of the tonsil (Fig. 9.31). During this part of the exposure, the lingual and hypoglossal nerves should be identified and displaced medially, but not overstretched or cut if possible. While it is relatively simple to preserve the hypoglossal nerve, this is not the case with the lingual nerve, which is frequently damaged unless it is released posteriorly at its origin from the mandibular nerve. Because of this, the patient must be forewarned of the probability of hemilignual anaesthesia following surgery.

At this stage, the exposure is complete and the tumour may be mobilized and removed by blunt dissection. This technique provides excellent exposure of the medial and superior aspects of the tumour which by any other method have to be approached blindly. The facial nerve is not necessarily identified but, if seen, should be carefully retracted laterally.

**Closure**

After removal of the tumour, it is prudent to cover the carotid arteries with an interposition flap fashioned from prevertebral fascia. This reduces the risk of a carotid blow-out if the wound dehisces and becomes infected. The mucosa is closed with a single layer of interrupted 3-0 Vicryl sutures and the mandible secured with the compression plates (Figs 9.32 and 9.33). The external wound is sutured in two layers with chromic catgut for the platysma and subcutaneous tissues and 4-0 nylon for the skin. A corrugated drain should be brought out through the inferior limit of the wound. Although some surgeons dispute the need for compression plates and rely on direct wires this is bad practice, unreliable and invites non-union. Indeed, in some cases, admittedly rare, it may be necessary to employ additional mandibular fixation, for example interdental wires or cap splints, to minimize the risk of non-union.

Though it may seem a minor consideration, it is easy to damage the teeth when carrying out a mandibulotomy and this can cause considerable dental disability for the patient and even give rise to medicolegal problems later. If this seems to be an overstatement, it is perhaps worth pointing out that damage to the teeth is the largest single cause of litigation against anaesthetists in the USA.

The drain should be removed after 48 hours and the sutures on the 7th postoperative day. If used, intermaxillary fixation or cap splints are usually kept in place for 4-6 weeks and are not removed until adequate bony union has been achieved.

**Advantages and disadvantages**

The major advantage of this technique is the exposure that it provides. Unlike other approaches, the medial, posterior and superior aspects of large tumours can be inspected directly. There is good control of the major blood vessels and removal of the tumour is not restricted by the styloid process, stylomandibular ligament or ramus of the mandible. These are considerable advantages but have to be weighed carefully against the disadvantages.

It is exceptionally difficult to determine from preoperative computerized tomography scans the precise nature of parapharyngeal masses. While magnetic resonance imaging has
helped distinguish neurofibromas from salivary neoplasms, the appearances of deep-lobe parotid tumours are not unlike those of meningiomas or metastatic nodes. From an oncological standpoint, the surgeon is performing little more than an enucleation with this technique which would be considered very unwise if the mass were situated in the superficial lobe of the parotid gland. There is rarely positive identification of the facial nerve which might therefore be inadvertently damaged, though admittedly this rarely happens. Traction on the lingual nerve often produces a temporary and sometimes permanent hemianaesthesia of the tongue, and as stated earlier, it is often impossible to preserve it. The time saved in removal of the tumour, which is initially so attractive with this technique, is lost later in the operation with closure. Finally, and perhaps most important, the morbidity for the patient in terms of a permanent lip-splitting scar together with potential dental injury, intermaxillary fixation and dietary restriction are considerable. While a patient should have completely recovered within two weeks after an uncomplicated lateral approach, the recovery period for a similar patient following a transmandibular approach might be anything up to three times longer.

Furthermore, if a deep-lobe tumour is so large that it proves impossible to deliver between the ramus of the mandible and the styloid process with a lateral approach, additional access can be made by one of two techniques. The mandible can be dislocated forwards, the styloid process fractured and the stylomandibular ligament transected, or alternatively, an osteotomy can be made in the ramus of the mandible as described previously, which is subsequently fixed by compression plates. There can be little doubt that either of these is aesthetically better than the midline mandibulotomy. Exponents of lateral osteotomies state that the inferior dental nerve deficits are uncommon and resolve in almost every case. It is for these reasons that the mandibular swing technique should be avoided, if possible. In the author's experience this approach has only been required on two occasions for the management of salivary gland tumours. The first was necessary when confronted with a massive palatal pleomorphic adenoma which was causing airway obstruction and extended from the base of the skull to the laryngeal inlet. The second was for the removal of multiple recurrences of a deep-lobe epimyoepithelial carcinoma which had developed in the medial pterygoid muscle some eight years after a primary total conservative parotidectomy and postoperative radiotherapy.

Radical Parotidectomy

Patient communication and consent

There are two essentials, first to warn the patient thoroughly about damage to their facial nerve and its consequences, and second, to warn of the risk of recurrence of the tumour. In the clinical situation where a radical parotidectomy has become necessary, it is important to emphasize to the patient that the results of their surgery may well be disfiguring but that this is the price that has to be paid for what may be a life-saving measure. This is not a step to be taken lightly and the decision to sacrifice the nerve should only be taken when there is clear histological evidence of the aggressiveness of the tumour and signs of involvement of the facial nerve at or before operation. Sacrificing the nerve when there is no evidence of its involvement at operation does little to improve prognosis and merely makes the patient's remaining life miserable. The histological nature of the tumour may be evident from intraoperative frozen sections, reliable fine-needle aspiration biopsy (where available) or even
as a result of a previous operation when for example, a misguided attempt has been made to remove what appears to be a sebaceous cyst behind the angle of the jaw, but a malignant tumour has been found.

In the unlikely event that the fully informed patient finds the possibility of facial palsy totally unacceptable then preservation of the facial nerve must be attempted. Even so it must be explained to the patient that, even with the best will in the world, some motor deficit may be unavoidable. In addition, it needs to be pointed out that (even though facial nerve function may be unimpaired at the time of consultation), facial palsy can result later from involvement of the nerve by tumour if an attempt is made to preserve it.

In this very difficult area it is essential to have written evidence of fully informed consent to avoid claims and medicolegal complications.

It is hard enough for surgeons to have to see, again and again, patients whom they have disfigured by facial palsy. However, it is difficult for the surgeon fully to appreciate how disabling and embarrassing this disability is for the patient who has to bear it through every day of life. In addition to the distortion and inappropriate movements of the face, there can be conjunctivitis from deficient lid movement and exposure keratitis from inadequate lubrication. Alternatively or in addition, in those patients whose facial nerves have been repaired by grafts, lacrimation may accompany eating or be unpredictable and uncontrollable. Sudden weeping of one eye can for example, make driving difficult or dangerous. In the worst cases, the embarrassment caused by drooling of saliva may be sufficient to deter the patient from eating in public.

It may, incidentally, be suggested that sacrifice of a facial nerve involved in a malignant tumour has not been shown to improve the prognosis. Evidence for this proposition has come from study of the management of adenoid cystic carcinomas. Such tumours may infiltrate the facial nerve so far back that total excision is impractical. However, even if it is accepted that preservation of the facial nerve does not worsen the prognosis of adenoid cystic carcinomas, this decision cannot be applied blanket-fashion to other, more rapidly growing tumours with equal expectation of a satisfactory outcome.

In yet other cases, the expectation of life may be so short that preservation of an infiltrated nerve may make little difference. It may then be felt to be unacceptable to increase the misery of the patient's remaining days with a facial palsy.

There can therefore be no completely hard and fast rules about sacrificing the facial nerve. All that can be said is that, unless there are overwhelmingly strong reasons against so doing, it should be sacrificed as part of a total parotidectomy for a malignant tumour in a patient who otherwise has a reasonable expectation of life. In reality, there are few occasions when this dilemma of having to sacrifice a functional facial nerve has to be faced.

Operative procedure

The extent of the resection in a radical parotidectomy is variable, and the dividing line between what is termed 'radical' by some and 'supraradical' by others is ill-defined. The resection nearly always includes either a suprathyroid or radical neck dissection. If the
overlying skin is infiltrated or has been previously breached by biopsy, it too must be included. Removal of the maxillary tuberosity, ramus of the mandible and mastoid process or petrous bone are supraradical procedures frequently justified by the extent or aggressive nature of the salivary malignancy. As each resection is tailored to an individual patient only those general points that need to be considered will be discussed further.

**Incision**

An extended 'lazy S' incision or 'Y' from which an inferior limb is dropped to the junction of the outer one-third and medial two-thirds of the clavicle is usually adequate. However, each case must be assessed on its own merits and modifications made to the incision in order to fulfil individual requirements. For example, skin removal or skin preservation in a previously healthy irradiated neck, a McFee neck incision might seem more appropriate (Fig. 9.34).

**Re-animation**

It is sometimes possible to preserve peripheral branches of the facial nerve to the mouth and eye but attempts to do this must not compromise the adequacy of the resection. More and more often, surgeons are employing immediate nerve-grafting techniques to re-animate the face. The sural nerve, located immediately behind the lateral malleolus, is easy to harvest and very suitable as a graft for the facial nerve. Up to 20 cm of sural nerve can be obtained from the lower leg either through a curvilinear or multiple horizontal stab incision. It can be divided into its constituent fascicles for peripheral anastomosis while leaving the main trunk to be sutured or approximated to the proximal stump of the facial nerve (Figs 9.35 and 9.36). While waiting for the graft to take and facial function to be restored, the eye must be protected. A lateral tarsorrhaphy or the insertion of a gold weight into the upper eyelid are simple and very effective methods.

Some surgeons still use a temporalis muscle transfer for facial re-animation. In this procedure, a long strip of temporalis muscle is mobilized, split and tunnelled through the eyelids to be attached firmly to the medial canthal ligament. If necessary, additional length can be obtained by suturing fascial slips to the muscle strips. This avoids mobilization of the muscle below the zygomatic arch and jeopardizing its blood supply. Other strips of the temporalis muscle can be firmly attached to the fascia beneath the vermilion border of the lip to prevent drooping of the oral commissure. At the time of surgery, both the eyelids and mouth must be overcorrected to a considerable degree. If this is not done, drooping of the mouth and eyelids will persist and no active movement can be produced by muscle retraining.

**Surgery for Recurrent Benign Disease**

There are no hard and fast rules concerning the management of recurrent benign disease, which in the vast majority of cases is pleomorphic adenomas. Every patient presents a slightly different problem according to the pattern of their recurrence and past surgical history. It is as well to be realistic with regard to the patient's ultimate prognosis. The surgeon should be continually aware that no matter what is done, approximately 30% of these patients will develop a further recurrence or recurrences, and that with every surgical intervention the risk of permanent damage to the facial nerve increases.
It is possible to suggest broad guidelines for the surgeon in this difficult aspect of salivary surgery, according to adequacy, or otherwise, of treatment.

**Inadequate treatment of primary lesions**

Patients who have previously had inadequate treatment (for example, enucleation, minimal limited excision, incomplete excision or open biopsy) should have at least a superficial parotidectomy or, if necessary, a total conservative parotidectomy, together with excision of the previous incision. Recurrences found in close proximity to branches of the facial nerve should be dealt with on their own merits, preserving the nerve if at all possible.

**Adequate treatment of primary lesion**

In patients who could be considered to have had adequate treatment for their primary lesion (for example, superficial, total conservative or radical parotidectomy) recurrences are probably best dealt with as isolated lesions. For instance, nodules within the scar can be managed by excision of the scar only with no attention being necessary to the parotid bed. An isolated recurrence elsewhere in the field is probably better dealt with by a limited resection. If a branch of the facial nerve is easily recognized then it is reasonable to attempt to dissect it clear of the recurrence, if that is feasible. However, all too often the operative field consists of dense scar tissue in which little more than the recurrence can be identified. In these circumstances, it is better to let the nerve take its chance and to warn the patient that this is preferable to the probability of further recurrence from inadequate removal, and also of unnecessary damage to more proximal branches of the facial nerve.

Sadly, there are still patients who present with confluent recurrences which at surgery are found to encase the facial nerve trunk and its main branches. For these, radical parotidectomy will probably be unavoidable though the author has salvaged some, quite spectacularly and unexpectedly, by using nerve monitoring. Particular attention should be directed to the deep surface of the zygomatic arch and mandible, as in these areas occult extensions of disease can be overlooked. If the main trunk of the facial nerve is sacrificed, it is best to perform an immediate nerve graft or re-animation procedure.

**Pediatric Parotidectomy**

Resection of the parotid gland in children is rarely necessary, but is most often indicated for developmental disorders, for example first branchial arch anomalies, cystic hygroma and vascular abnormalities. However, both benign and malignant salivary gland tumours are found in children and > 60% of these arise within the parotid gland. The surgery of both types of disease is slightly more difficult in children than in adults for the following reasons:

➤ The facial nerve is smaller and courses more superficially within the parotid in children than in adults. This is partly due to incomplete development of the mastoid process which leaves the stylomastoid foramen and its contents, the facial nerve, relatively unprotected at the base of the skull. As a result, the nerve may be encountered at a very early stage in the surgical procedure and can be inadvertently damaged.
➤ First branchial arch anomalies of the collaural type run lateral, deep to or between the branches of the facial nerve in their passage from the external auditory meatus to the angle of the jaw. Usually the child or young adult will have experienced numerous infective episodes within the fistulous tract before they present to the surgeon. The parotid gland adjacent to the fistula is densely scarred and the plane of dissection around the facial nerve may have been destroyed. Iatrogenic facial weakness or paralysis is a very significant risk in these patients, and is a complication about which their parents should be very clearly forewarned.

➤ Other developmental disorders are notoriously difficult to dissect, for example cystic hygromas and vascular anomalies. These lesions are either so diffuse or bleed so easily that surgical landmarks can be lost and as a consequence accidental damage to the facial nerve be incurred.

The use of a facial nerve monitor for this type of surgery cannot be recommended too strongly. Not only does it predict the impending proximity of the facial nerve trunk, but it also helps minimize trauma to its finer branches which can be irrevocably damaged all too easily. It hardly needs repeating that facial palsy is a devastating handicap to carry through life, both for the child, its parents and the surgeon who inflicts it.

Injuries to the Parotid Duct

Salivary fistulae are caused by facial lacerations or parotid surgery. The majority are transient in nature and close spontaneously. Most surgeons’ experience of this complication is limited and therefore the advice proffered in many reports is almost anecdotal. However, few substantial series have been reported. In these it is apparent that the site of injury is important in determining the most appropriate management for the patient and their likely prognosis. Glandular fistulae are more likely to seal spontaneously than fistulae from the parotid duct. Various treatments have been proposed for those that do not close within a few weeks. Tympanic neurectomy, auriculotemporal neurectomy, cautery, irradiation and intravenous nutrition have all been advocated and found to be equally successful. Fluid restriction together with a period of intravenous nutrition, is the least meddlesome option and should be tried before resorting to others.

If the main duct is transected in a facial wound it is advisable to undertake primary repair. The severed duct should be sutured with 8-0 Vicryl and splinted with a silicone tube which can be inserted through the mouth and secured to the buccal mucosa. This is not a simple procedure and is best performed with a microscope. In late cases with well-established fistulae, it may be simpler to re-implant the duct directly into the mouth. Fistulae which are resistant to all methods of treatment should be considered for total conservative parotidectomy.
Surgery of the Submandibular Gland

Indications

Resection of the submandibular gland is indicated for neoplasms or intractable infection. The gland should also be removed as part of a radical or suprathyroid neck dissection for the control of locally invasive or metastatic squamous-cell carcinoma arising within the oral cavity, pharynx or larynx.

Preoperative investigations

In the case of calculi, plain lower occlusal and lateral jaw radiographs are useful to determine their position and number (Figs 9.37-9.39). These may be combined with sialography to determine the state of the ductal system in patients with recurrent inflammatory disease. Computerized tomography imaging is indicated for patients with submandibular neoplasms in which fixation or infiltration of the mandible and tongue musculature is clinically suspected. Radiographic evidence of localized infiltration or erosion is an indication for a wider excision to include a partial glossectomy or rim resection of the mandible. A chest radiograph is mandatory for all cases of known or suspected malignant disease but, with certain tumour types, may not contraindicate local surgery even if metastatic spread is present.

The role of fine-needle aspiration biopsy has been discussed previously.

Informed consent

The patient should be reassured that a properly placed skin incision is unlikely to leave a cosmetically unsightly scar. Damage to the marginal branch of the facial nerve may result in either a temporary or permanent weakness of the angle of the mouth which will be most noticeable on smiling and puckering the lips. In cases of malignant disease involving or abutting this nerve, it may be necessary to resect it, together with the gland, and thereby inflict a permanent deficit (Fig. 9.40).

Neuropraxia of the lingual and hypoglossal nerves is unusual but possible, especially in those patients who have sustained numerous infective episodes. In these cases the gland is likely to be densely tethered to adjacent structures which become more difficult to identify and preserve. Planned resection of these nerves is necessary in locally advanced malignant disease and will result in hemianaesthesia of the anterior two-thirds of the tongue and limitation of tongue movements. Sensory deficit in the presence of malignant disease is usually tolerated well by the patient, but is a common source of litigation in those with benign or inflammatory pathology. Motor dysfunction of the tongue initially impairs articulation and mastication but the patient rapidly compensates. Ultimately the tongue muscles waste on that side but without further symptomatic deterioration.

Surgical Anatomy of the Submandibular Gland

The submandibular salivary glands consist of a large superficial lobe and a smaller deep lobe. These are continuous around the posterior border of the mylohyoid muscle. The medial aspect of the superficial part lies on the inferior surface of the mylohyoid muscle and
is covered there only by the oral mucosa. The lateral surface is covered by the body of the mandible, while its inferior surface rests on both bellies of the digastric muscle. Its inferior surface is covered by the platysma muscle, deep fascia and skin. The anterior facial vein runs over the surface of the gland within this fascia, but the facial artery, for most of its early course, is related to the deep surface of the gland until it ultimately runs adjacent to the anterior facial vein superficially. Posteriorly, it is separated from the parotid by a condensation of deep cervical fascia - the stylohyoid ligament. The deep part of the gland lies on the hyoglossus muscle where it is related superiorly to the lingual nerve and inferiorly to the hypoglossal nerve and deep lingual vein. The capsule of the gland is well defined and is derived from the deep cervical fascia which splits from the greater cornu of the hyoid bone to enclose it. For the surgeon this is an easy plane to find and dissect.

The duct of the gland is formed by the union of several tributaries and is about 5 cm in length. It emerges from the middle of its deep surface and runs in the space between the hyoglossus and mylohyoid muscles to the anterior part of the floor of the mouth, where it opens onto a papilla to the side of the lingual frenulum. In its anterior part it is related laterally to the sublingual glands and may receive many of their ducts. During its course on the hyoglossus muscle it is crossed from its lateral side by the lingual nerve. This is a most important surgical point in duct relocation procedures. The lingual nerve must be disentangled from the duct at its crossing point otherwise inadvertent damage may result.

The submandibular gland receives its blood supply from branches of the facial and lingual arteries. Venous drainage accompanies these vessels. There are several lymph nodes immediately adjacent to the superficial part which drain the gland and adjacent structures. Multiple parasympathetic secretomotor fibres are distributed from the submandibular ganglion which hangs from the lingual nerve and may occasionally be easily observed at surgery. Preganglionic fibres join the lingual nerve from the chorda tympani.

**Operative procedure**

General anaesthesia with either an oral endotracheal tube, secured to the contralateral side of the mouth, or nasal tube, is used. In previously infected cases a prophylactic broad-spectrum antibiotic is given intravenously at the start of the operation. Patients should be placed on the operating table in the supine, reverse Trendelenburg position with the neck extended by means of a sandbag placed beneath the shoulders, and their face turned away from the operator and the side of the lesion. The skin should be carefully cleansed with a disinfectant soap solution and the area draped with head, side and body towels. Dissection is considerably facilitated by preliminary infiltration of the skin and subcutaneous tissues with 40-50 mL of a 1:200,000 solution of adrenaline, but this is not an essential prerequisite if there is a cardiovascular contraindication to its use.

The incision is outlined with a skin marking pen (Fig. 9.41). It should be made to lie in a natural skin crease approximately 2.5 cm below the lower border of the mandible and extending for approximately 10 cm anterior to the sternomastoid muscle. The incision is deepened through the platysma muscle and flaps developed in the fascial plane immediately beneath it. The superior flap is extended to the body of the mandible, taking care not to damage the marginal mandibular branch of the facial nerve which runs in the same tissue plane (Figs 9.42 and 9.43). The nerve enters the neck 1 cm in front of the angle of the
mandible, loops over the facial artery and vein up to 2 cm below the lower border of the body of the mandible before sweeping superiorly to the angle of the mouth. The inferior flap is developed to the level of the body of the hyoid bone.

If there is no concern about invasion of the mandibular branch of the facial nerve, it can be protected from inadvertent damage by one of two manoeuvres. The facial vessels can be transected at a low level on the surface of the submandibular gland and reflected superiorly (Figs 9.44 and 9.45). The nerve, which lies lateral to the facial vessels, can thereby be lifted out of the operative field. Alternatively, the capsule of the gland can be opened at the level of the hyoid bone and dissection continued beneath it. The elevated capsule protects the nerve in a similar fashion to the first technique. Occasionally, it is very difficult to identify the mandibular branch, and in these cases a nerve stimulator or monitor with sensing electrodes inserted into the orbicularis oris is helpful.

The superficial part of the gland is then mobilized by either blunt or sharp dissection and retracted posteriorly in order to expose the deep portion which lies on the hyoglossus muscle and is partly covered by the mylohyoid muscle (Figs 9.46 and 9.47). The facial vessels are ligated as necessary if this has not already been accomplished or there are significant branches to the gland itself. Retraction of the mylohyoid anteriorly, together with posterolateral traction on the gland, brings the lingual nerve, duct and more proximal part of the facial artery into the operative field (Figs 9.48 and 9.49). The lingual nerve appears as a ribbon-like band loosely attached to the body of the gland by a few fibres - the parasympathetic secretomotor supply. Section of these fibres releases the nerve from the gland and permits it to assume a more superior relation. At this stage, the hypoglossal nerve may be seen inferior and parallel to the lingual nerve but is sometimes partially covered by the posterior belly of the digastric muscle. The proximal part of the facial artery is usually ligated at this point.

The gland is then further mobilized from the hyoglossus muscle and about its duct so that this may be ligated and transected as far anterior as possible (Figs. 9.50 and 9.51). Failure to attend to this detail may leave behind troublesome paraductal salivary tissue which is exceptionally difficult to eradicate by subsequent surgery. It is thought that the mucoid secretions of these paraductal glands are very viscous and that they stagnate and eventually calcify in the remnant of Wharton's duct. Recurrent and symptomatic calculi have been reported in the residual duct many years after primary surgery. An alternative explanation is that these calculi were overlooked at the time of initial surgery and present again when sufficiently large enough to obstruct the sublingual glands. In the light of these reports, it would seem prudent to carefully palpate the duct for the presence of calculi and ensure that any found are removed with the gland or delivered into the mouth.

The operative field should be irrigated with normal saline and perfect haemostasis achieved. A small vacuum drain is inserted and brought out through the skin posteriorly. The wound is closed in two layers with 3-0 chromic cat gut or Vicryl subcutaneously and 4-0 monofilament nylon for the skin. The drain is removed on the first postoperative day and the skin sutures after one week.
Surgery of the Submandibular Duct

Indications

The main indication for surgery to the submandibular duct is the removal of distally situated, but otherwise easily accessible, calculi. Patients with multiple strictures of the ductal system, recurrent or multiple stones, are better treated by total resection of the gland.

Preoperative Investigations

Plain radiographs of the floor of the mouth and lateral neck are essential. Patients who have had previous multiple infective episodes should have sialographic evaluation of the duct system.

Informed consent

The patient should be warned of the possibility that infection may recur or that at operation the stone may fall back into the body of the gland and become inaccessible. Exploration of the posterior portion of the duct by a transoral approach may damage the lingual nerve and cause a temporary or permanent sensory deficit of the anterior two-thirds of the tongue on that side.

Operative procedure

Calculi at the orifice of the duct may be removed under local anaesthesia provided by a lingual nerve block or local infiltration of 2% lignocaine with 1:80,000 adrenaline. Ducts containing multiple calculi or with stones relatively far back in the mouth are better explored under general anaesthesia delivered through a nasal endotracheal tube.

The mouth and face are cleansed with a disinfectant soap solution and the head and neck draped. Gags or interdental props are inserted to maintain the mouth open. A sling suture is inserted around the duct proximal to the calculus and tensioned sufficiently to prevent the calculus slipping back into the gland. The area of the distal duct is then infiltrated with a 1:200,000 solution of adrenaline. The duct is then either cannulated with a fine probe and opened along it so that the calculus can be removed (Figs 9.52 and 9.53), or an incision is made directly over the calculus. 4-0 resorbable sutures are placed so that the duct orifice is marsupialized to the floor of the mouth (Figs 9.54-9.57).

The patient is instructed to rinse their mouth with hot isotonic saline solution three times each day for the first postoperative weeks (Figs 9.58 and 9.59).

Surgery for Sialorrhoea

Sialorrhoea (drooling) is a distressing complaint most often seen in children with cerebral palsy or adults with acquired bulbar palsy, strokes or Parkinson's disease. Many of the children with cerebral palsy are also severely epileptic and this adds to the management difficulties as discussed later. The fundamental disorder is that of neuromuscular incoordination, patients being unable to swallow or control their saliva rather than having an
excess. It is easy to underestimate the social impact of this condition on even mildly affected patients. These individuals frequently perceive their drooling as the main cause of social isolation whether or not this is the case. Parents of severely affected children may need to change their child's clothing many times every day or submit their child to long-term hospitalization.

**Preoperative assessment and conservative therapy**

A multidisciplinary approach to assessment and management is essential. Speech therapists, physiotherapists, dental surgeons and otolaryngologists can all make valuable contributions. Surgery should only be contemplated after a period of intense conservative therapy and prolonged observation. It is also inadvisable to operate on children under the age of six years, as drooling may improve spontaneously with further development. Close attention should be paid to the correction of abnormal body posture, dental malocclusion and nasal obstruction. All of these worsen drooling but are easily correctable. Such capacity as there is to initiate and complete swallowing should be maximized by appropriate sensory training.

In some patients, behavioural modification by auditory evoked conditioned reflexes has been found to be helpful. Commercially available devices (dribbling boxes) consist of a collecting box containing a sensor. The box is placed beneath the child's chin and bleeps each time saliva drips into it. The success of all conditioning and postural therapy has been found to be largely dependent on the intellectual capacity of the patient, the age at which therapy is started as well as on other disorders or disabilities that may be associated.

Pharmacotherapy with anticholinergic drugs may be helpful in a few, but in general, the side-effects of these drugs (constipation, urinary retention, impaired visual accommodation and often, agitation) only compound the patient's troubles.

**Surgical treatment**

Surgical approaches to the control of drooling that have been proposed range from excision of the major glands and denervation procedures, to relocation or ligation of the salivary ducts. The submandibular salivary glands, as the major contributors to resting salivary flow, have received most attention in this respect. Naturally, all operations have to be undertaken bilaterally. This is therefore a serious consideration in treatment planning as these procedures are major undertakings even in normal patients, let alone those with neurological disabilities.

The results of denervation by section of the chorda tympani nerve, through a tympanotomy approach, are disappointing. Only 50-80% of patients are reported to achieve a satisfactory outcome and even some of these regress with time because of neural regrowth. Bilateral tympanotomy is inevitably attended by a period of hearing loss until middle ear exudates have dissipated. Nerve sections therefore have to be undertaken as staged procedures in order to avoid this period of temporary deafness. Furthermore, section of the chorda tympani automatically leaves a deficit of taste to the anterior two-thirds of the tongue and therefore the operation has largely become obsolete.
Although some still advocate bilateral resection of the glands, the majority now agree that equally good results can be obtained by relocation of their ducts. There are significant advantages to both the patient and surgeon from duct relocation of which the most obvious is the avoidance of the potentially distressing effect of inadvertent marginal nerve damage on the oral competence of a cerebral palsied child.

**Submandibular Duct Relocation. Operative Procedure.**

**Preparation**

The operation of submandibular duct relocation is performed under general anaesthesia with a nasal, endotracheal tube and small pharyngeal pack. A pack that is too large and bulky makes the procedure very difficult indeed. A broad-spectrum antibiotic given with the premedication is a sensible precaution and should be continued for at least one week.

**Operative technique**

The surgeon is seated at the head of the table with an assistant at his side to retract the tongue as required. The floor of the mouth is infiltrated with 1:200,000 adrenaline. An elliptical island of mucosa is incised around the submandibular papillae and by blunt dissection, the individual ducts and lingual nerves are identified (Figs 9.60 and 9.61). The island is then divided (Figs 9.62 and 9.63) and a submucosal tunnel created on each side of the floor of the mouth to open at the base of each tonsillar fossa approximately 1 cm behind the anterior pillar of fauces (Figs 9.64 and 9.65). A fine rubber sling or silk suture is pulled back through the submucosal tunnel to exit at the initial incision (Figs 9.66 and 9.67). The mucosal cuff surrounding each duct orifice is sutured to the sling, which is then used to pull the duct to its final position in the tonsillar fossa where it is secured with a resorbable suture (Figs 9.68 and 9.69). The anterior incision is also closed with resorbable, interrupted sutures.

**Postoperative care and complications**

Most patients develop swelling of the floor of the mouth which normally subsides within 2-3 days, but has on rare occasions compromised the airway and necessitated intubation. Intravenous access for fluid replacement and drug administration is frequently necessary postoperatively until a normal diet is established and patients can take drugs by mouth. This is rarely necessary for more than 24-48 hours as the majority of patients are fit for discharge home by the third postoperative day. However, it has to be emphasized that there must be no doubt that epileptics are fully stabilized before discharge.

Two complications are regularly encountered: ranula formation and submandibular duct obstruction. Crysdale and White (1989) reported an 8% incidence of postoperative ranula formation in their series of 194 patients. The frequency of this complication prompted them to modify their technique and resect all sublingual tissue at the time of relocation.

Late obstruction of relocated submandibular ducts has been attributed to excessive tonsil size and recurrent tonsillitis. Surgical removal of these obstructed and rerouted glands has been found to be difficult because of adhesions. Bailey and Wadsworth (1985) claim to have circumvented this complication by resiting the duct at the base of the anterior pillar.
rather than within the tonsillar fossa. Obviously enough, patients with a long-standing history of tonsillar infection should have a tonsillectomy some weeks before relocation.

**Prognosis**

The results of treatment by submandibular duct relocation are difficult to interpret. Reduction in the severity of drooling should be achieved in at least 80% of patients, but that is not synonymous with the cessation of sialorrhoea. Saliva is still present on the chins of ≤ 70% of those cases deemed by the surgeon to be successful. Success is therefore very difficult to assess and greatly depends on the expectations of the patient or parents. At one extreme, a patient may be happy with a minor improvement in drooling despite persistence of saliva on the chin; at the other, the patient may cease drooling as a result of removal of the major glands but be made unhappy by the discomfort of a dry mouth.

Bilateral submandibular gland excision and parotid duct ligation is claimed to be more effective than submandibular duct relocation alone. Certainly salivary flow is substantially reduced by this technique, but at the cost of external scarring and sometimes a distressingly dry mouth with its attendant risk of orodental infection. Surprisingly, postoperative parotid swelling has been neither invariable nor troublesome. Brody (1989) has cautioned against this procedure in patients with severe athetosis. In his experience, their tongue movements whipped the thickened residual saliva into an intensely adherent and fetid gum which became plastered to the lips and teeth. Brody felt that this complication was worse for patients and their families than the original sialorrhoea and caused him to abandon ablative surgery for drooling in athetoid patients.

In summary, surgical treatment should be tailored for each particular patient and not undertaken until all other potential influences have been properly addressed. There is always much to commend a single surgical intervention for any individual. Patients with incessant, drenching sialorrhoea should therefore be considered for more radical therapy than those less severely affected. Nevertheless, whatever the procedure adopted, it is important first to warn patients or parents that it may be a major undertaking and, second, to caution them against any excessive hopes of total cure.

**Surgery of the Sublingual Glands**

**Indications**

There are two conditions affecting the sublingual glands that necessitate surgical attention: tumours and ranulae. The detailed technique of sublingual tumours is identical to those of the submandibular gland and therefore will not be repeated later in this section.

**Preoperative investigations**

Well-circumscribed or relatively small lesions do not require diagnostic imaging, but in view of the propensity of tumours to be malignant at this site, fine-needle aspiration cytology is advisable. Extensive cysts, which on clinical grounds are suspected to be plunging ranulae, or tumours with any degree of fixation, are better evaluated by MRI. An external approach is indicated for any ranula which has a significant component within the submental
and submandibular triangles of the neck.

**Informed consent**

The patient should be warned about possible anaesthesia of the anterior two-thirds of the tongue which can be caused by damage to the lingual nerve where it is intimately related to the submandibular duct.

**Surgical Anatomy of the Sublingual Salivary Glands**

The sublingual salivary glands lie in the anterior part of the floor of the mouth, between the mucous membrane, the mylohyoid muscle and the body of the mandible close to the symphysis, where it may produce a small depression - the sublingual fossa. It has numerous excretory ducts which either open directly onto the mucous membrane or into the terminal part of the submandibular duct.

**Ranulae**

**Preparation**

The operation is performed under general anaesthesia with a nasal endotracheal tube and small pharyngeal pack. Systemic, broad-spectrum antibiotics are given with the premedication if there has been a history of repeated infection and should be continued for at least one week.

**Operative technique**

The surgeon is seated at the head of the table with an assistant at the side to retract the tongue. It should be the intention of the surgeon to completely excise the ranula rather than marsupialize it, as this reduces the chance of further problems. The floor of the mouth is infiltrated with 1:200,000 adrenaline to provide a blood-free field and to facilitate dissection. Cannulation of the submandibular duct at this stage is a wise precaution as it serves to indicate the course of the duct and the likely position of the lingual nerve, which passes deep to the duct. The ranula is then separated from the floor of the mouth by blunt dissection.

Occasionally the ranula will be found to extend further along the lateral border of the mylohyoid muscle than was anticipated. Complete resection of this type of cyst is not possible by an intraoral approach alone. It is then necessary to open the submandibular triangle as described for resection of the submandibular gland. At least the cervical component of plunging ranulas are mucous extravasation cysts and need to be handled with extreme care. It is all too easy to rupture them at a premature point in the operation. Collapse of the cyst makes subsequent dissection extremely difficult and remnants are then often left behind which give rise to recurrences.
Surgery of Palatal Tumours

The three factors that determine the surgical management of palatal tumours are:

➤ The histological nature of the tumour.

➤ The size and extent of the tumour.

➤ The age and general health of the patient.

Precise knowledge of the histological nature and malignant potential can be obtained by incisional biopsy and the extent of the tumour by clinical examination and computerized tomography scans. The amount of tissue that need be removed with the tumour is variable. For example, a small adenoid cystic carcinoma of the palate in a relatively young patient would indicate an extensive resection because of the extensive malignant potential of the tumour. This resection might include the alveolar ridge, nasal septum, posterior aspect of the maxilla, together with a clearance of the pterygopalatine and infratemporal fossae. In general the surgeon should aim to obtain a tumour-free margin of about 2 cm for all malignant tumours. On the other hand, a palatal pleomorphic adenoma in an elderly patient could be adequately treated by a more localized excision leaving the palatal bone intact. In patients with a longer life expectancy, this conservative approach for certain benign tumours would be inappropriate and a limited removal of underlying bone (palatal fenestration) should be undertaken.

It is fortunate that the palate is almost the only site where preoperative incisional biopsy is not contraindicated. Surgical excision of palatal tumours always includes the overlying mucosa and therefore, in contrast to the major glands, preliminary biopsy does not predispose to recurrence or influence long-term results.

Operative Technique. Local Excision of Benign Tumours.

It must be emphasized that this approach to the management of palatal tumours should be reserved for those tumours with little potential to recur, for example, neurofibromas and haemangiomas. A special case can occasionally be made to treat some adenomas in elderly patients by this technique. The resection is performed under general anaesthesia with either an oral or nasal endotracheal tube. Patients should be positioned on the operating table in the supine position with a sandbag placed beneath their shoulders to extend their head and neck. This allows the surgeon to sit at the patient's head, which is immobilized and suspended in extension by a mouth gag and Draffin rods. The table may need to be tilted slightly head down to obtain a perfect view of the tumour and surrounding tissue. Preliminary infiltration of the area with 2% lignocaine with 1:80,000 adrenaline solution provides an almost bloodless field.

An incision is made around the tumour down to the periosteum, with an adequate margin of normal palatal tissue to ensure a complete lateral excision (Fig. 9.70). The tumour is then removed by developing a plane between the periosteum and the palate with an elevator. The defect can be left open to heal by secondary intention, a process that may take
several weeks or even months. Alternatively, it can be protected by an acrylic dental appliance adequately relieved in the area of the resection to retain a Coe-pak dressing. Some surgeons favour closure by rotation flaps based on either the greater palatine artery, or from the buccal mucosa where the blood supply is derived from the submucous plexus and underlying facial muscles. The palatal flap should be raised parallel to the dental arch and extended posteriorly to a point 1 cm anterior to the greater palatine foramen (Fig. 9.71). The periosteum beneath the flap is not raised. The flap is rotated and sutured into position with 3-0 Vicryl sutures on a round bodied needle. The residual defect at the donor site may be closed by advancement of a buccal flap, covered by a free graft, held in position by a bolster or acrylic dental appliance, or left to granulate (Fig. 9.72).

Small, benign tumours confined to the soft palate are excised using an elliptical incision made in the long axis of the palate (Fig. 9.73). An adequate cuff of underlying muscle must be included. Parallel, mucosal relieving incisions facilitate primary closure of the defect with 3-0 Vicryl mattress sutures and prevent excessive shortening of the palate (Fig. 9.74).

Operative Technique. Palatal Fenestration.

Removal of palatal bone is mandatory for all malignant tumours and should be seriously considered for those benign tumours which have a tendency to recur or have already recurred after a local excision. Small or localized growths are easily managed by fenestration, while extensive tumours or those with a reputation for advanced early spread, for example adenoid cystic carcinoma, necessitate a more extensive resection or maxillectomy.

Before surgery the patient should be assessed by a dental surgeon. An appliance (obturator) must be made to cover the operative defect, allow the patient to eat normally and prevent nasal regurgitation during the immediate postoperative period. For partially or completely edentulous patients, minor adjustments can be made to their existing denture to enable an obturator to be attached. Prosthetists require some time to construct these appliances and therefore allowance should be made for this when planning surgery.

Preparation of the patient for fenestration is identical to that described for local excision. Some surgeons, however, prefer to work from the front of the patient and use dental props and cheek retractors to keep the patient's mouth open. An incision is made around the tumour and incorporates a margin of healthy tissue. The adjacent mucoperiosteum of the healthy palate is elevated and retracted. Cuts are made in the palatal bone beneath this retracted periosteum with either an osteotome or fine oscillating saw. The tumour, in continuity with the palate, floor of the nose or maxillary antrum are then gently eased out of the mouth by cutting any deep attachments. The periosteum is then allowed to fall back into the operative defect and any bone edges that it fails to cover are cut back further (Fig. 9.75).

Small defects in the palate may sometimes be closed with local flaps, as described in the previous section. The majority of defects, particularly those which include the entire length of the soft palate, are not closed and at this point the prosthodontist should fit the obturator and make sure that it is well retained. It is very important that it does not fall out or become displaced easily. If this should happen immediately after surgery it could obstruct the airway or at a later stage be a constant source of discomfort to the patient. In some, adequate
adhesion of the obturator to the palate is achieved, but in others either clasps to remaining teeth are necessary to provide sufficient retention or a two-part, interlocking device can be made which uses the cavity to its fill retentive capability. In a few patients, additional temporary anchorage is necessary and can be easily provided by circumzygomatic wires fixed to cleats on the buccal side of the denture.

**Postoperative care**

The prosthesis is usually left in place for 7-10 days and then removed, cleaned and adjusted under mild sedation. Further modifications and adjustments are made at weekly intervals until the area has healed completely and the palatal contour stabilized. At that time, a definitive appliance is made and fitted. A speech therapist should be encouraged to contribute to the postoperative management of the patient. Their skill in the rehabilitation of speech and swallowing is often greatly appreciated.

**Note**

1. Friedrich Trendelenburg (1844-1924), Leipzig surgeon. Thought to be the first surgeon to carry out a pulmonary embolectomy.