The Pathology and Surgery of the Salivary Glands

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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)

I. *Adenomas*
- Pleomorphic adenoma
- Myoepithelioma (myoepithelial adenoma)
- Basal cell adenoma
- Warthin's tumour (adenolymphoma)
- Oncocytoma (oncocytic adenoma)
- Canalicular adenoma
- Sebaceous adenoma
- Ductal papilloma
  - Inverted ductal papilloma
  - Intraductal papilloma
  - Sialadenoma papilliferum
- Cystadenoma
  - Papillary cystadenoma
  - Mucinous cystadenoma

II. *Carcinomas*
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade (terminal duct) adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Basal cell adenocarcinoma
- Sebaceous carcinoma
- Papillary cystadenocarcinoma
- Mucinous adenocarcinoma
- Oncocytic carcinoma
- Salivary duct carcinoma
- Adenocarcinoma (not otherwise specified)
- Malignant myoepithelioma (myoepithelial carcinoma)
- Carcinoma in pleomorphic adenoma (malignant mixed tumour)
- Squamous cell carcinoma
- Small-cell carcinoma
- Undifferentiated carcinoma
- Other carcinomas

III. *Non-epithelial tumours*

IV. *Malignant lymphomas*

V. *Secondary tumours*

VI. *Unclassified tumours*

VII. *Tumour-like disorders*
- Sialadenosis
- Oncocytosis
- Necrotizing sialometaplasia (salivary infarction)
- Benign lymphoepithelial lesion
- Salivary gland cysts
- Chronic submandibular sialadenitis (Küttner tumour)
- Cystic lymphoid hyperplasia in AIDS.

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 dictinctive 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 consideration, 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 adjacently. 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 (Eveson 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

Alcoholism
Diabetes mellitus
Other endocrine diseases
Pregnancy
Drugs; particularly sympathomimetics
Bulimia
Idiopathic.

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.