Salivary Gland Neoplasms

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1. Note about the Authors

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2. Self-Assessment Quiz

1. Why is it not possible to perform a total parotidectomy?
2. Name the five areas of distribution of the facial nerve.
3. What is a dumbbell tumor of the parotid gland?
4. What is the value of sialography?
5. Why were recurrences of mixed tumors frequent prior to 1941?
6. Do lymph nodes occur within the parotid gland?
7. What important structures pass through the deep "lobe" of the parotid gland?
8. What is the most common location of minor intraoral salivary glands?
9. Which is the most common bilateral tumor of the parotid gland?
10. What is the significance of pain in parotid tumors?
11. Name the cell of origin of the myxoid elements of a mixed tumor.

12. Name two tumors in which the cells contain abundant mitochondria.
13. What malignant salivary tumor tends to spread along nerve sheaths?
14. What is the most common benign parotid tumor in children?
15. What is the most common type of carcinoma to develop in a preexisting mixed tumor.

3. History

Little was written about the salivary glands up to the middle of the 17th century. In 1660, Niels Stensen (1638-1686) discovered and described the parotid duct, named after him. Thomas Wharton in 1656 identified the submandibular gland and duct and Bartholinus, in 1669, the sublingual gland. Early operations on the parotid gland were reported by Siebold in 1781, Abernathy in 1815, Carmichael in 1818, Gensoul in 1824, and Lisfranc in 1826.

The first operation using ether inhalation anesthesia was performed for the removal of a parotid tumor by Dr John C Warren in 1846. In 1868, Erichsen advocated preservation of the facial nerve when excising parotid tumors. The first attemt at "total" parotidectomy with preservation of the nerve was made by Codreanu in 1892. Sir Frederic Treves stated that total parotidectomy is anatomically impossible. Our current knowledge of the incomplete encapsulation of the parotid and its variable extensions in the parapharyngeal region and on the cheek suggests that total resection is indeed not feasible.

Blair in 1912 devised a technique for tumor removal with preservation of the nerve. Using local anesthesia, he performed cautious dissection while observing facial twitching caused by nerve stimulation, which permitted preservation of the nerve fibers.

Sistrunk in 1921 stressed the importance of exposing the facial nerve before removing parotid tumors. He identified the mandibular branch, lifted the gland away from the nerve and resected the gland with the enclosed tumor. In spite of this report, there persisted great reluctance to perform parotidectomy due to the risk of facial nerve injury - a common occurrence at that time.

High recurrence rates were reported following local excision of mixed tumors. The use of escharotics intraoperatively and of radiation postoperatively failed to improve results. McFarland noted that recurrence rates after removal of small tumors were higher than with larger tumors, and actually suggested a waiting period to allow tumors to "ripen". The high recurrence rate suggested to some that benign mixed tumors were "multicentric" in origin and that radical or total parotid resections were necessary.

In 1941 reported a technique whereby superficial and deep lobes were resected with preservation of the nerve. Starting at the anterior border of the gland, the lower branches of the nerve were isolated, traced posteriorly to the main trunk, which was followed forward as it branched to allow total removal, first of the portion superficial to the nerve, then of the portion deep to the nerve.

Martin and others advocated routine exposure of the main trunk of the facial nerve at the stylomastoid foramen as the initial step in the procedure. The practice of extracapsular resection of parotid neoplasms after nerve exposure gradually became the standard surgical treatment of parotid neoplasms.

Proper treatment of salivary gland tumors demands thorough familiarity with the anatomy of the region and an understanding of the pathology and clinical behavior of the neoplasms peculiar to the salivary glands.

The first clinical description of a parotid tumor was by Kaltschmeid in 1752. A classification of salivary gland tumors based on gross morphology was advanced by Berard in 1841. A detailed histologic description of tumors composed of mixed elements was first offered by Billroth, who also described and named the cylindroma. Virchow in 1863 gave the first exhaustive histologic classification of salivary tumors. The term "mixed tumor" referring to the most common salivary neoplasm, was introduced by Minssen in 1874 and is still used today.

In 1910, Albrecht and Artz described a histologically independent type of tumor, papillary cystadenoma lymphomatosum. In 1929 Warthin reported two cases of this lesion and Martin and Ehrlich attached the eponym "Warthin's" to the tumor, the name by which it is best known in this country.

Foote and Becker in 1945 described mucoepidermoid tumors, and Foote and Frazell in 1954 presented a comprehensive classification and description of the different tumors of the salivary glands. They described acinic cell tumors for the first time and assigned the name adenoid cystic carcinoma (a term they attributed to Ewing) to the adenocarcinoma previously called cylindroma. With slight modifications their classification is the one most widely used today.

4. Salivary Gland Development

Most authors believe that salivary gland development is the same for all salivary glands. The anlagen arise initially as ectodermal budes from the lining of the stomatodeum - the primitive oral cavity. These initially solid buds "invade" deeper mesenchyma and are separated from each other by a basal lamina or membrane similar to that seen in the development of teeth, hair follicles or other epithelial derivatives. As this invagination or penetration occurs the ectodermal tissues become surrounded by mesenchymal elements, leading to generalized tissue-to-tissue interactions. This is followed by two major developmental processes - cytodifferentiation, or a degree of cellular specialization and morphogenesis, consisting of cellular reorganization into a precise pattern for function. As this penetration into deeper mesenchyme occurs, there is elongation of the main duct primordium, most likely related to cell proliferation along its length and not merely an increase in cell number at the proximal and distal ends of the duct. As development progresses, budding of the ends of the primordia takes place and becomes more pronounced.

In the 5-month fetus a differential rate of cell division occurs within the outer layer of columnar cells leading to canalization or lumenization, creating the characteristic lobular architecture. Fundamental to the maintenance and stabilization of this lobular pattern is the

presence of the basal lamina and of nonfibrillar mesenchymal collagen and acid mucopolysaccharides adjacent to the developing glandular elements. Bannerjee noted loss of lobular morphology in the submandibular gland subsequent to degradation of basal lamina by hyaluronidase, demonstrating that the ectodermally derived basal lamina acts as a substratum to which ectodermally derived cells may attach and adhere as development proceeds.

As branching morphogenesis proceeds, acinar differentiation occurs by a change in the terminal tubular elements. This anatomical organization of cords and tubules along with end clusters or alveoli place salivary glands into the group of compound tubular-alveolar glands.

Progression of the branching phase of development resembling the arborization or ductal tree pattern with lobular end bulbs is associated with differentiation of intercalated and striated ducts. Further development is characterized by further cytodifferentiation of acinar and ductal elements and the establishment and maintenance of the duct and acinar luman. Secretion of water and electrolytes by these cells maintains the patency of the developing ductal system.

Coinciding with the early formation of acinar secretory granules there can be noted the presence of flattened cellular elements, presumably myoepithelial cells, between the acinar elements and basal lamina. Varying in configuration from stellate- to spindle-shaped, these cells, at their early stages of development, lack the characteristic myofilamentous arrays of the mature myoepithelial cell and are often optically clear. It is thought that myoepithelial cells develop from stem cell differentiation of terminal tubular elements that retain mitotic capability until they mature into myosin-containing cells within the first postpartum week.

5. Anatomy

Salivary Gland Unit

The functional element of salivary glands of all types may be termed the salivary gland unit. The overall functional anatomy of serous, mucous, and mizxed types of glands may be considered as being generally similar, although individual anatomical differences in acinar and ductal configuration are well recognized.

Pyramidal-shaped acinar cell elements surround a central lumen into which salivary fluid is deposited by a process of exocytosis. The process of secretion is strongly dependent on the function of the myoepithelial cells that are posed between the base of the acinar cells and the supportive stroma. After reaching the acinar lumen, the salivary secretion enters the intercalated portion of the duct system, which in minor and sublingual glands may be quite short. Cells of the intercalated ducts are cuboidal in shape and may contain secretory granules. Intercalated ducts are followed by striated ducts, composed of tall columnar or prismatic cells with central nuclei. Short microvilli demonstrate deep membrane invaginations which are in close association with mitochondria and have a perpendicular orientation to the cell base. As the striated duct leaves the intralobular area it connects with the excretory or interlobular duct. A slow alteration in lining cell morphology is evident as the duct orifice is approached, where a simple columnar lining blends into a stratified columnar type. Basal (reserve) cells along the duct system are small and cuboidal and interlock with the overlying duct lining cells.

Parotid Gland

Proper performance of surgery of the parotid gland requires a thorough understanding of the anatomy of the gland and its variations. The intimate relationship between the facial nerve and its branches and the parotid gland makes difficult adequate resection of the gland with preservation of the nerve.

The parotid gland is the largest of the salivary glands, weighing between 15 and 30 gm. It is composed of multiple lobules separated by interlobular fascial septa and is nearly a pure serous-secreting gland. It is roughly pyramidal in shape and occupies an irregular space between the external auditory canal, mastoid process, and sternomastoid muscle posteriorly; the ascending ramus of the mandible, over which it spills and overlaps, anteriorly; and the styloid process with the muscle attached to it, the digastric muscle, the transverse process of the atlas and the pharyngeal wall, medially. The lateral surface of the parotid is covered by the dense parotid fascia, an extension of the anterior layer of deep cervical fascia. The fascia is attached superiorly to the zygomatic arch and posteriorly to the anterior border of the sternomastoid muscle. These two attachments form barriers to extension of salivary gland tissue beyond them. As the fascia extends anteriorly onto the cheek, it thins out into loose areolar tissue, and in this region the anterior limits of the parotid gland, lying on the masseter muscle, are variable and difficult to define. The inferior portion of the parotid gland ("tail" of parotid) is ill defined and extends into the cervical region, sometimes for a considerable distance. It is for this reason that tumors arising from the "tail" of the gland may present in the mid-neck, in front of the sternomastoid muscle.

The parotid fascia thickens inferiorly to form the stylomandibular ligament, which separates the submandibular gland from the parotid. The dense fascia overlying the parotid resists expansion and thus is the cause of pain when parotid swelling occurs rapidly, and of the failure of fluid collections (blood, pus) to fluctuate or "point" beneath the overlying skin.

The medial extension of parotid tissue is also extremely variable. Although the cervical fascia splits to envelop the gland, the medial portion of the fascia is thin and often incomplete. For this reason, lobules of parotid salivary tissue, either attached or separate from the main body of the gland may lie deep to the temporomandibular joint and the lateral pterygoid muscle, and on the pharyngeal wall.

The extension of parotid gland to the parapharyngeal space explains the occasional occurrence of dumbbell tumors of the deep "lobe" of the parotid, which present in the tonsillar or palatal regions. Patey and Thackray describe a "stylomandibular tunnel" through which the dumbbell tumor extends to the parapharyngeal region. The tunnel is formed by the base of the skull above, the ascending ramus of the mandible and medial pterygoid muscle in front, and the styloid process and styloglossus muscle behind. On its deeper plain, the tunnel enlarges and is bounded by the superior constrictor muscle of the pharynx. As described by Chu and Stravitz, tumors extending parapharyngeally produce medial displacement of the tonsils and palatal arches, and project intraorally. The mucosa overlying these tumors is mobile. Access to the parapharyngeal space is difficult, especially when this space is filled with a deep-lobe parotid tumor. McLean and Berdal advocate transection of the mandible anterior to the angle in order to deliver such tumors intact. Nanson divides the

styloid process and the stylomandibular ligament and, by applying pressure on the intraoral protrusion of the tumor, delivers it into the cervical wound.

The anterior portion of the parotid is grooved by the posterior margin of the mandible and extends over the surface of the masseter. From the tip of this extension there emegres the parotid duct (Stensen's duct) along which there may occur a prolongation of the gland. Sometimes this projection is detached from the main parotid, forming an accessory parotid gland which is at times the site of inflammation or involvement by salivary tumors. The accessory gland may be above or below the duct and may empty into the main duct by one or more accessory ducts, which are demonstrable on sialography and must be ligated to prevent fistula when accessory glands are resected. Frommer found 8 detached accessory glands in 96 cadaver dissections. Perzik found 46 of 591 parotid neoplasms within an accessory gland.

The parotid duct is about 5 cm in length, runs along the line drawn from the tragus of the ear to the middle of the upper lip passes over the masseter, turns medially at its anterior border, and pierces the buccinator muscle to open into the buccal mucosa.

Relationship of Facial Nerve to Parotid Gland. Early anatomical studies described the parotid gland as a bilobed structure consisting of a larger, superficial and smaller, deep lobe connected by an isthmus, with the facial nerve lying in a connective tissue plane separating the two lobes. Bailey agreed with this concept and stated that "the facial nerve runs through the parotid gland like meat through a parotid switch". McKenzie refuted the bilobar theory. He injected the duct system and by careful dissection found the portions of the gland superficial and deep to the nerve had numerous communicating ducts, that there were numerous "isthmi" bridging gaps between nerve branches, and that even when a fascial plane seemed to bisect the gland into lobes, the nerve usually did not pass in this plane, but seemed to penetrate the substance of one or other lobe. Winsten and Ward confirmed the unilobular structure by x-ray studies of ducts injected with opaque material and by detailed embryological studies. They believed that rather than a "parotid sandwich", the nerve could be compared to a "creeper vine weaving itself into the meshes of a trellis-work" parotid fence.

The facial nerve emerges from the skull at the stylomastoid foramen, just posterior to the base of the styloid process, passes downward, giving off postauricular and digastric branches, and curves anterolaterally to enter the posterior border of the parotid gland very shortly after leaving the foramen. Within the parotid, 1 or 2 cm after penetrating the gland, the nerve divides into two main trunks as it traverses lateral to the posterior facial vein. The major divisions, temporofacial and cervicofacial, continue forward and further subdivide into a variable number of terminal branches which innervate the muscles of facial expression. The distribution and position of the terminal branches and their intercommunications were studied and analyzed by Davis. Although generally categorized as five branches (temporal, zygomatic, buccal, mandibular and cervical), these can be more properly described as five areas of distribution. Dissection of 350 specimens demonstrated 8 patterns of nerve distribution. In the average adult, the exit of the facial nerve from the stylomastoid foramen is at a point about 1 cm above the tip of the mastoid process and 1-1.5 cm deep to its anterior border. In childrenthe foramen is more superficial. The level within the parotid gland at which the nerve bifurcates into its main divisions is 2.5-3.5 cm above the angle of the mandible, or about two thirds of the distance between the angle and the temporomandibular joint. The temporofacial

division is larger, often twice the size of the cervicofacial division. As seen in the figure, the branches of the upper division are usually more complex and anastomose more often. Because of these anastomoses, spontaneous recovery of partial facial paralysis can occur when one or more peripheral branches are sacrificed.

Greater Auricular Nerve. This sensory nerve is the largest branch of the cervical plexus (from C3). It ascends from the middle third portion of the posterior border of the sternomastoid muscle across its lateral surface to traverse vertically the posterior portion of the parotid gland close to the external jugular vein. The branches to the ear lobule are usually preserved in parotidectomy, while the facial and mastoid branches are divided.

Blood Vessels Within the Parotid Gland. The anterior facial vein, accompanying the facial artery, crosses the inferior margin of the mandible deep to the lower branches of the facial nerve and joins the posterior facial vein, which lies deep to the parotid gland or passes through the gland near the angle of the mandible. The crossing of the anterior facial vein by the mandibular branch of the facial nerve which is fairly constant, is used by some surgeons as a landmark for dissection of the nerve. The external carotid artery enters the deep portion ("deep lobe") of the parotid almost immediately after emerging from beneath the posterior belly of the digastric. The artery runs superiorly, just deep to and parallel to the posterior facial vein and divides within the parotid into its two terminal branches, the maxillary going deep to the neck of the mandible and the superficial temporal artery passing in front of the tragus of the ear. The auriculotemporal nerve (containing parasympathetic fibers that control salivary secretion) lies just behind the superficial temporal artery near the tragus of the ear. Injury to this nerve interrupts the autonomic nerve supply to the salivary gland and may result in gustatory sweating, often called Frey's syndrome. The transverse facial artery, a branch of the superficial termporal artery, courses with its accompanying vein beneath the superficial portion of the parotid just inferior to the zygomatic process, close to the zygomatic branch of the facial nerve.

Although large arteries and veins pass through the parotid, the gland itself is not a highly vascularized organ, and splitting the parotid tissue results only in minor bleeding. Patey describes a fasciovenous plane, ie, the chief veins form a plexus just deep to the facial nerve and its branches. By dissecting just superficial to this venous plexus, the surgeon can resect the portion of the parotid superficial to the facial nerve in an almost avascular plane.

Lymph Nodes Related to the Parotid Gland. The parotid gland contains 20-30 lymph follicles and lymph nodes connected by a rich lymphatic network. In addition, there are numerous nodes located in a paraglandular position, superior, posterior, and inferior to the parotid, but not anterior to the gland. These lymph nodes, within and in the vicinity of the parotid gland, are often the sites of metastases from malignant tumors arising in the temple, scalp, postauricular area, brow, cheek, auricle, and auditory canal. The most frequently encountered tumors are squamous cell carcinoma, melanoma, and parotid salivary gland tumors. Presence of a focus of metastatic parotid carcinoma in an intraparoti node does not necessarily imply involvement of lymph nodes lower in the neck.

Aberrant or heterotopic salivary gland tissue (acini and/or ducts) is commonly found within lymph nodes in and around the parotid gland, as first reported by Neisse. Careful dissection of 19 newborn infants revealed salivary gland tissue in intraparotid lymph nodes

in all cases. The histogenesis of papillary cystadenoma lymphomatosum (Warthin's tumor) within such heterotopic tissue is discussed below. Enlargement of such lymph nodes due to hyperplasia or neoplasia of the contained salivary tissue sometimes assumes clinical significance and must be considered in the differential diagnosis of parotid gland tumors.

Submandibular Gland

The submandibular triangle is an isosceles triangle with the base formed by the horizontal ramus of the mandible and other sides by the anterior and posterior bellies of the digastic muscle. It is occupied by the major portion of the submandibular salivary gland and associated lymph nodes. Its outer surface is covered by an extension of the investing layer of the deep cervical fascia which splits to enclose the submandibular gland, thinning out to attach loosely to the mandibular ramus. This fascia is much thinner than the one covering the parotid gland.

The anterior facial vein crosses on the surface of the gland, sometimes passing through its substance to unite with the posterior facial vein behind the gland. The facial artery ascends into the triangle from a point medial to the mandible in front of the angle, passes through or grooves the upper portion of the submandibular gland to cross the horizontal ramus of the mandible at around its midpoint and thence obliquely onto the cheek. The mandibular branch of the facial nerve crosses the facial artery and vein just above or below the lower border of the mandible.

The floor of the submandibular triangle is composed of the mylohyoid muscle anteriorly and the deeper hyoglossus muscle posteriorly. The lingual veins (usually two) accompany the hypoglossal nerve, which courses under the posterior belly of the digastric and stylohyoid muscle to lie horizontally on the lateral surface of the hyoglossus. The nerve passes between the mylohyoid and hyoglossus to enter the undersurface of the tongue. The lingual artery lies deep to the hyoglossus muscle and is not seen within the triangle. Higher on the surface of the hyoglossus, deep to the mandible, the lingual nerve traverses the floor of the triangle, passes below the duct and then crosses it medially to turn upward on the genioglossus muscle. From the lower border of the lingual nerve the submandibular ganglion (parasympathetic, with fibers derived from the facial nerve via the chorda tympani) is suspended by short rami, and the ganglion in turn is connected to the submandibular gland by postganglionic fibers.

The submandibular salivary gland, a paired structure, about one-half the size of the parotid gland, is roughly almond shaped and is a mixed seromucinous-secreting gland. The gland is a fairly well-encapsulated organ covered by loose areolar tissue. It can be reaidly lifted out of the triangle after its vascular and nerve connections have been divided. From the anterior tip of the gland, the submandibular duct (of Wharton) passes anteriorly above the mylohyoid muscle, and reaches the posterior end of the sublingual gland, forming an almost continuous mass. The duct first lies below, then medial to the sublingual gland, where it may receive a major sublingual duct (of Bartholin). Its terminal portion lies beneath the mucosa of the floor of the mouth and opens via a papilla just lateral to the frenulum.

The submandibular lymph nodes range in number from three to eight. In contrast to the parotid nodes they are never intraglandular in position. They are situated generally as a chain along the upper border of the submandibular gland, along or just below the mandible. The most constant are pre- and postvascular in relation to the facial vessels as they cross the mandibular ramus. Occasionally, there are nodes anterior or posterior to the submandibular gland onthe floor of the triangle or on the lateral surface of the gland. The submandibular nodes drain the facial nodes lying on the cheek along the facial vessels and receive afferent lymphatic vessels draining a large part of the face, the gingival mucosa, the buccal mucosa and the anterior portion of the tongue.

Sublingual Gland

The third largest salivary gland, the sublingual gland, a paired structure, is about one-half the size of the submandibular gland. It is a purely mucous gland. It lies beneath the mucosa of the floor of the mouth above the mylohyoid muscle, between the mandible laterally and the muscles of tongue medially. The submandibular duct passes along the medial border of the sublingual gland. Ten to 20 small sublingual ducts (of Rivinus) pass from the upper border of the gland to open into the floor of the mouth individually. Obstruction of one of the ducts results in a mucus-filled cyst, or ranula. Occasionally (less than 50% of cases) a larger sublingual duct (of Bartholin) joints the submandibular duct before its termination into the mouth. The sublingual artery, a branch of the lingual artery, supplies the gland.

Minor Salivary Glands

Intraoral minor salivary glands, nearly always purely mucous glands, number 450-750. They are located in the mucous membrane of the lips, cheeks, hard and soft palate, uvula, floor of the mouth, posterior part of the tongue, retromolar area and peritonsillar region. Additional glands identical to the intraoral glands can be found in the nasopharynx, larynx, paranasal sinuses and trachea. Aberrant salivary tissue is sometimes found in unusual locations and may give rise to neoplasms. Batsakis, reviewing the literature, recorded such salivary tissue in the body of the mandible, lower part of the neck, hypopharynx, middle ear, sternoclavicular joint and thyroglossal duct. He also stated that such aberrant glands may be found within the tonsils (1% of cases) and in lymph nodes of the head and neck area, besides those within the parotid gland.

The minor salivary glands are most abundant in the palate, numbering about 250 in the hard palate, 100 in the soft palate, and 12 in the uvula. They are arranged in an orderly manner in compact rows and seldom extend anterior to the level of the first molars. They are not present in the midline of the palate or in the gingiva laterally. They become larger and more numerous near the junction of the hard and soft palate and open individually into the mucous membrane via intercalated ducts.

According to Bhaskar et al, the glands of the palate, root of the tongue and glossopalatine region are purely mucous; the glands near the circumvallate papillae, purely serous; and the glands of the lips, cheeks, and accessory sublingual glands, mixed serous and mucus-secreting.

Histogenesis of Tumors

In assessing salivary gland neoplasms of epithelial origin one is struck by the similarity of adult salivary cell types to many of these neoplasms. several systems have been designed to explain tumor histogenesis based on light and electron microscopic features of the neoplasms.

The multicellular theory of origin considers that salivary epithelial neoplasms originate from the differentiated or adult cell counterpart from within the functional salivary complex, which includes the acini and the entire ductal system. Thus it follows that acinar cells will give origin to the acinic cell carcinoma, while striated duct cells produce oncocytic neoplasms. The intercalated duct cells may produce mixed tumors and adenoid cystic carcinomas with or without a myoepithelial cell component. Excretory duct elements are considered to be responsible for the development of mucoepidermoid and squamous cell carcinomas.

A second theory of tumor histogenesis has been defined as the basal reserve cell or progenitoc cell theory. Fundamental to this concept is the assumption that basal cells of the excretory and intercalated ducts function as progenitor or reserve cells for more highly differentiated components of the functional salivary complex.

Extension of the reserve cell concept to the unicellular pluripotential theory to explain formation of all tumor types fails to account adequately for neoplasms that arise within an intralobular location since only striated and intercalated ducts are found within these locations.

A more plausible variation or interpretation of the reserve cell theory has been termed the semipluripotential bicellular theory, in which the excretory duct reserve cell can produce or give rise to squamous or mucin-producing columnar cells, while intercalated duct progenitor cells may differentiate toward intercalated, striated or acinar elements. With the interaction between the mesenchymal or myoepithelial component and intercalated duct precursor elements a broad variation of tumor types may evolve. The role of either of these two types of biologically uncommitted or undifferenitated reserve cells, in addition to the myoepithelial cell as a modulating influence, serves as an explanation for the morphological variations of salivary tumors. Of further importance in acceptance of this histogenic theory is that it is not dependent on the dedifferentiation of rather highly specialized cellular elements and subsequent neoplastic growth. This bicellular theory has been supported by light microscopic studies and more recently by experience with ultrastructural techniques.

Brief consideration must be given to the myoepithelial cell in the development of certain salivary neoplasms, particularly as it relates to some recent studies that have included ultrastructural analysis. It is the myoepithelial cell that has been implicated as the element of mixed tumor, which, by virtue of its interaction with the epithelial component, provides the variable mesenchyme-like component of the lesion. Our ultrastructural studies as well as those of others have confirmed the presence of myoepithelial cells within the adenoid cystic carcinoma and demonstrated the presence of myoepithelial cells in oncocytoma and papillary cystadenoma lymphomatosum.

An extension of the putative role of the myoepithelial cell in the histogenesis of salivary gland tumors is the situation in which myoepithelial cells nearly totally comprise the neoplastic cell population. Such lesions, so-called myoepitheliomas of benign and malignant character, have been reportedly found in major and minor salivary glands.

Classification of Salivary Tumors

When considering terminology and classification of neoplastic diseases of salivary glands within an historical context much confusion arises. Foote and Frazell sought to institute a rationale for understanding the relationship between structure and behavior of salivary neoplasms, by proposing a brief, rather simplified classification (Table 1). This system was successful in that it provided a better understanding of the behavior of salivary gland tumors. Further refinement of histologic and nosologic criteria as well as the need for an internationally acceptable system of classification led to the formation of the World Health Organization scheme of salivary gland tumor classification (Table 2).

Table 1. Classification of Salivary Gland Tumors (Foote and Frazell)

- Mixed tumors
  - Benign
  - Malignant
- Mucoepidermoid tumors
  - Low-grade
  - High-grade
- Squamous cell carcinomas
- Adenocarcinomas
  - Adenoid cystic
  - Miscellaneous forms
    - Trabecular or solid
    - Anaplastic, mucous cell; or with pseudoamantine pattern
  - Acinic cell
- Papillary cystadenomata lymphomatosa
- Oxyphil adenoma
- Sebaceous cell adenoma
- Benign lymphoepithelial lesions
- Unclassified tumors
  - Benign
  - Malignant.

Table 2. WHO Classification of Salivary Gland Tumors

- Epithelial tumors
  - Adenomas
    - Pleomorphic adenoma (mixed tumor)
    - Monomorphic adenomas
      - Adenolymphoma
      - Oxyphil adenoma
      - Other types

Mucoepidermoid tumor
Acinic cell tumor
Carcinomas
Adenoid cystic carcinoma
Adenocarcinoma
Epidermoid carcinoma
Undifferentiated carcinoma
Carcinoma in pleomorphic adenoma (malignant mixed tumor).

A simplified, rather workable system devised by Eneroth (Table 3) was based on a large series (2.513 patients) in which benign and malignant lesions were typed. Studies of other investigators, using large numbers of cases with careful follow-up information, have allowed a better understanding of the biology and behavior of salivary gland tumors.

Table 3. Classification of Salivary Gland Tumors (Eneroth)

Benign
Pleomorphic adenoma
Papillary cystadenolymphoma
Oncocytoma
Malignant
Carcinoma in pleomorphic adenoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Acinic cell carcinoma
Mucus-producing adenopapillary carcinoma
Solid undifferentiated carcinoma
Epidermoid carcinoma

Most recently Batsakis (Table 4) has formulated a very detailed classification system based on histomorphological criteria. Within this system the potential confusion and controversy regarding acinic cell and mucoepidermoid lesions is avoided by not considering these entities as "tumors" but rather as carcinomas, a concept we favor wholeheartedly. Additionally, clear cell tumors are dealt with as either benign or malignant lesions, while the basal cell adenoma is considered as a precursor of the pleomorphic adenoma as originally suggested by Feyrter. Allowance is made for inclusion of recently described entities such as the epithelial-myoepithelial carcinoma of intercalated duct origin, which has a predilection for early lymph node metastasis. Further study of the more recently described entities include within this system will enable a better understanding of their biologic characteristics and clinical behavior. The true malignant mixed tumor, while very rare, is considered separately from the carcinoma ex pleomorphic adenoma or malignant transformation of a previously benign pleomorphic adenoma. In the malignant mixed tumor of salivary gland origin, a truly biphasic malignant pattern is noted, while in the carcinoma ex pleomorphic adenoma the epithelial malignancy is usually a ductal carcinoma and behaves as such.

Table 4. Classification of Epithelial Salivary Gland Tumors (Batsakis 1979)

Benign
- Mixed tumor (pleomorphic adenoma)
- Papillary cystadenolymphomatosum (Warthin's tumor)
- Oncocytoma - oncocytosis
- Monomoprhic adenomas
  - Basal cell adenoma
  - Glycogen-rick adenoma
  - Clear cell tumor
  - Myoepithelioma
  - Others
- Sebaceous lymphadenoma
- Papillary ductal adenoma (papilloma)
- Benign lymphoepithelial lesion

Malignant
- Carcinoma ex pleomorphic adenoma
- Carcinoma arising in/from a mixed tumor
- Malignant mixed tumor
- Mucoepidermoid carcinoma
  - Low-grade
  - Intermediate grade
  - High-grade
- Adenoid cystic carcinoma
- Acinous cell carcinoma (acinic carcinoma)
- Adenocarcinoma
  - Mucus-producing adenopapillary and nonpapillary carcinoma
  - Salivary duct carcinoma (ductal carcinoma)
- Oncocytic carcinoma (malignant oncocytoma)
- Clear cell carcinoma (non-mucinous and glycogen or non-glycogen containing)
- Primary squamous cell carcinoma
- Hybrid basal cell adenoma/adenoid cystic carcinoma
- Epithelial/myoepithelial carcinoma of intercalated ducts
- Undifferentiated carcinoma
- Miscellaneous (including sebaceous, Stensen's duct, melanoma and carcinoma ex lymphoepithelial lesion)
- Metastatic.

Radiation Etiology

Swelstad et el reviewed several reports of increased incidence of salivary gland tumors following irradiation in infancy and childhood and documented 13 salivary gland tumors and 8 parathyroid adenomas in 18 patients with a history of previous radiotherapy to the head and neck. Eight of these patients also had associated thyroid neoplasia. Ju reported 5 cases of salivary gland tumors 15-25 years following radiation therapy for acne, hemangioma, eczema or overgrowth of hair. Takeichi et al observed a significant increase in incidence of salivary gland tumors, especially malignant ones, among subjects exposed to atomic radiation in Hiroshima, the incidence being proportional to the proximity to the hypocenter of explosion.

Schneider et al traced 1.922 cases of patients who had received small doses of radiation to the tonsils and nasopharynx in childhood. They found four malignant and six benign salivary gland tumors occurring prior to age 24. Belsky et al made a detailed study of survivors 12--25 years after exposure to atomic radiation (over 300 rad) and found the risk of development of salivary gland tumors to be ninefold that in the nonirradiated controls.

Incidence

Salivary gland tumors comprise 3% of all neoplasms in the head and neck. The incidence is between 1 and 2 per 100.000 population. The tumors are reported to be more common in some racial groups. In Malaysia the proportion of salivary gland tumors to all tumors is 4.1% in Malays, 2.3% in Chinese, and 1.7% in East Indians; in the USA the incidence is higher in blacks than in whites. The sex incidence is about equal in most series.

Salivary gland tumors occur most frequently in the parotid gland (75-85% of cases). Thackray estimated that for every 100 parotid tumors there were 10 in the submandibular glands, as shown in Table 5, 10 in the minor salivary glands and one in the sublingual gland. The site distribution varies in different countries. Parotid tumors constitute 75% of salivary gland tumors in England, 63% in Malaya, 57% in South Africa and 52% in Uganda. The proprtion of salivary gland tumors occurring in the submandibular gland varies from 13.7% in England to 30% in the Chinese population in Malaya.

Table 5. Percentage Distribution of Different Epithelial Tumor Types in The Parotid and Submandibular Glands

	Parotid		Submandibular	
	Middlesex	Karolinska	Middlesex	Karolinska
	651	2158	60	170
Adenomas				
Pleomorphic adenoma	72.0	76.2	68	60
Monomorphic adenoma				
Adenolymphoma	9	4.7	1.7	2.4
Oxyphylic adenoma	0.6	1	0	0.6
Other types of adenoma	1.8		0	
Mucoepidermoid tumors	2.3	4.1	0	3.6
Acinic cell tumors	1.2	3	0	0.6
Carcinomas				
Adenoid cystic carcinoma	3.3	2.3	17	15
Adenocarcinoma	1	2.4	1.7	0
Epidermoid carcinoma	1	0.3	3.3	7
Undifferentiated carcinoma	3.7	3.9	6.6	9
Carcinoma in pleomorphic adenoma	4.1	1.5	1.7	1.8.

Tumors may arise in the minor salivary glands of the oral cavity; about one-half of intraoral salivary neoplasms occur in the palate, the remainder are found in the lips, cheeks, uvula, floor of mouth, posterior tongue, retromolar area, and peritonsillar region. Similar

neoplasms may occur in other sites that contain glandular elements identical to intraoral glands, such as the nasopharynx, larynx, lacrimal glands, paranasal sinuses, trachea, skin and breast.

Aberrant salivary glands may rarely occur in unusual areas, such as the body of the mandible, middle ear, and sternoclavicular joint, as well as in association with branchial vestiges in the lower part of the neck. Neoplasms, usually malignant, have been reported in all of these sites.

The incidence of tumors arising in the sublingual and minor salivary glands is higher in subjects living in the West Indies than elsewhere. Salivary gland tumors of the palate occur more frequently in Uganda (19.3% of all salivary tumors) and South Africa (29%), but much more rarely in Sheffield (7.5%) and Malaya (5.5%). Spiro, in an excellent study of 492 cases of tumors of minor salivary origin, noted the sites of origin as shown in Table 6; 36.8% occurred in the palate.

Table 6. Sites of Origin of Minor Salivary Gland Tumors (Spiro et al, 1973)

	No	%
Palate	181	36.8
Antrum	67	13.6
Tongue	54	11
Cheek or lips	49	10
Nasal cavity	47	9.6
Gingival	29	5.9
Floor of mouth	17	3.5
Larynx	15	3
Tonsil	11	2.2
Nasopharynx	10	2
Ethmoid	8	1.6
Oropharynx	4	0.8
Total	492	100.

The incidence of the various benign and malignant tumors of the parotid gland in three large series is shown in Table 7. The incidence of malignant minor salivary tumors is shown in Table 8.

Table 7. Parotid Gland Tumors: Histologic Diagnoses in Reported Series

Classification	Foote and Frazell N = 766	Bardwill N = 153	Eneroth N = 736
Mixed tumor			
Benign (pleomorphic adenoma)	447 (57.6)	36 (23.5)	569 (70.9)
Malignant (biphasic malignancy)	46 (5.9)	34 (22.2)	
Papillary cystadenoma lymphomatosum (Warthin's tumor)	50 (6.4)	5 (3.3)	41 (5.1)

Mucoepidermoid carcinoma			
Low-grade	45 (5.8)	32 (20.9)	34 (4.2)
High-grade	45 (5.8)		
Adenoid cystic carcinoma	16 (2.1)	13 (8.5)	19 (2.4)
Acinous-cell (acinic) carcinoma	21 (2.7)	8 (5.2)	36 (4.5)
Adenocarcinoma (miscellaneous)	32 (4.1)	16 (10.4)	17 (2.1)
Oncocytic-cell tumor	1 (0.1)	1 (0.7)	4 (0.5)
Squamous-cell carcinoma	26 (3.4)	8 (5.3)	1 (0.1)
Miscellaneous			
Benign	3 (0.4)		
Malignant			15 (1.8)
Unclassified			
Benign	4 (0.5)		
Malignant	30 (3.9)		

Note: Numbers in parentheses represent percentages.

Table 8. Incidence of Malignant Minor Salivary Gland Tumors (Batsakis)

	No of Cases	Percent Malignant
Reynolds et al	49	69
Brown et al	38	63
Chaudhry et al	1.414	54
Smith	38	37
Edwards	23	31
Stuteville and Corley	80	91
Bardwill et al	100	87
Shumrick	54	93
Potdar and Paymaster	110	50.

Clinical Picture

Parotid tumors generally present as asymptomatic, slow-growing, solitary, well-defined mobile masses lying either below the ear lobule and behind the ascending ramus of the mandible, or on the cheek, lying below the zygomatic arch and on the masseter muscle overlying the ascending ramus. Benign tumors generally evolve slowly over a period of years and malignant tumors have a shorter history and more rapid growth. Pain usually signals a malignant neoplasm, but not invariably. We have seen several patients who have a history of sudden appearance of a mass that in two instances was associated with a "popping" sensation or sound. This occurs when a tumor lying in the narrow space behind the jaw reaches a critical size and suddenly exists to the surface.

Mixed tumors and early malignancies are firm to hard, lobulated and mobile. Warthin's tumors often lie low in the tail of the parotid and are soft or semifluctuant. Invasive carcinomas are fixed and poorly encapsulated. In advanced cases, bone, skin or the ear may be involved. As noted below, nerve involvement usually implies a malignant tumor.

Parotid tumors situated behind or below the mandible can be rolled over the border of the bone; in contradistinction, submandibular tumors cannot be maneuvered in this manner. The position of a parotid tumor relative to the facial nerve cannot be determined clinically although deep lobe tumors are often less mobile. Deep lobe tumors presenting in the palate, tonsillar region or nasopharynx can often be ballotted on bimanual examination.

Submandibular gland tumors should be examined bimanually, with one finger in the floor of the mouth, the other below the mandible. This permits better appreciation of their size and mobility and often distinguishes salivary neoplasms from lymph node enlargement.

Clinical characteristics relative to special tumor cell types will be discussed in the appropriate sections dealing with the individual tumors.

The Facial Nerve in Neoplastic Diseases of the Parotid Gland

The extracranial portion of the facial nerve passes through the parotid gland, entering the gland as a single trunk, dividing within the gland, and emerging from its anterior border as five to nine terminal branches. Aside from trauma, the nerve is rarely paralyzed by nonneoplastic conditions. In a 20-year period at the Karolinska Institute, only one instance of facial nerve paralysis occurred after chronic parotitis.

The presence of paralysis along the distribution of the facial nerve in combination with a parotid mass is almost always pathognomonic of a malignant neoplasm. Rarely, facial nerve palsy has been reported with benign mixed tumors. In a series of 877 cases of salivary gland tumors, Frazell found no instance of facial nerve palsy in a patient with a benign tumor. None of 1.780 patients with benign salivary gland tumors reviewed by Eneroth had persistent facial nerve paralysis. Although in rare instances other causes of facial nerve paralysis (Bell's palsy, middle ear cholesteatoma, neurologic diseases) may coexist with a benign parotid tumor, it is generally accepted that facial nerve paralysis associated with a parotid gland tumor is diagnostic of a malignant tumor. The reported incidence of facial palsy with malignant parotid gland tumors varies from 8% to 26%. Of a total of 378 malignant tumors reported by Eneroth, spontaneous facial nerve paralysis occurred in 46 (12%). In 6 of these 46 patients, the paralysis was the first and only symptom of parotid carcinoma. Conley et al also found spontaneous facial paralysis in 12% of 279 patients with parotid gland malignancy. Black noted that in 3 instances facial palsy preceded presence of tumor mass by intervals of 7 months, 16 months and 33 months.

In one reported instance, the correct diagnosis of acinic cell carcinoma of parotid was made only when an attempt to decompress the facial nerve revealed invasion of the nerve as it passed through the bony canal within the temporal bone.

Pain may be present due to nerve involvement by tumor. This feature was present in 43% of 65 patients with parotid cancer in whom the facial nerve had to be sacrificed. Pain is rarely a clinical finding in patients with benign salivary gland tumors. Rarely, pain may be the first symptom of carcinoma of the parotid gland.

Preoperative facial paralysis in parotid gland malignancy indicates a poor prognosis regardless of treatment. Eneroth followed 46 such patients with no instance of cure. Nearly all (45 of the 46) died of their tumor with survival varying up to 13.8 years and an average survival of 2.7 years. In his study the single surviving patient was alive with tumor at 10 years. Conley reported 26% 5-year survival and 12% 10-year survival rates in patients with parotid malignancies presenting with facial nerve paralysis.

Staging of the Carcinoma of the Parotid Gland

There are several staging systems for carcinomas of the parotid gland; however, the system of Spiro, a practical one, is the one we generally use.

Staging System for Carcinoma of the Parotid Gland - Spiro

T	Primary tumor
T_1	Tumor up to 3 cm, solitary, freely mobile; intact facial nerve.
T_2	Tumor 3.1-6 cm, solitary, freely mobile, or with reduced mobility or skin fixation; intact facial nerve.
T_3	Tumor 6 cm, or with multiple nodules, or ulceration, or deep fixation, or facial nerve dysfunction.
N	Regional lymph nodes
N_0	Regional lymph nodes not palpable.
N_1	Movable homolateral nodes considered to contain growth.
N_2	Movable contralateral or bilateral nodes considered to contain growth.
N_3	Fixed nodes.
M	Distant metastasis
M_0	No evidence of distant metastasis.
M_1	Distant metastasis present.

Stage I	$T_1N_0M_0$
Stage II	$T_2N_0M_0$
Stage III	$T_3N_0M_0$
	Any T_1N_1
Stage IV	Any T_1N_2 or N_3M_0
	Any T_1; any N_1M_1.

Differential Diagnosis of Salivary Gland Tumors

In addition to tumors of the parotid gland, numerous neoplasms of nonsalivary orign may be found in the "parotid space". In a series of 700 parotidectomies, Nussbaum et al found 98 such cases, or 14% of the total. These are summarized in Tables 9 and 10.

Table 9. Tumors Arising in (Intraparotid and Periparotid) Lymph Nodes (Nussbaum et al, 1976)

Neoplastic	
Primary	
Malignant lymphoma	16
Metastatic	
Melanoma	2
Colonic carcinoma	1
Tonsillar carcinoma	1
Lymphoepithelioma	1
Total metastatic neoplasm	5
Inflammatory	
Hyperplastic lymph nodes	19
Tuberculosis	8
Actinomycosis	1
Infectious mononucleosis	1
Cat scratch fever	1
Sarcoidosis	2
Toxoplasmosis	1
Total inflammatory	33
Total (lymph node disease)	54

Table 10. Tumors of Somatic Origin (Nussbaum et al, 1976)

Skin and appendages	
Benign	
Epidermoid inclusion cyst	2
Sebaceous lymphadenoma	1
Branchial cyst	1
Malignant	
Sebaceous gland carcinoma	1
Total skin	5
Muscle and connective tissue origin	
Benign	
Lipoma	18
Fibroadenoma	1
Desmoid tumor	1
Granular cell myoblastoma	1
Hypertrophy masseter muscle	1
Malignant	
Fibrosarcoma	1
Myxosarcoma	1
Total muscle and connective tissue	24

Vascular origin	
Hemangioma	4
Venous aneurysm	1
Cystic hygroma	1
Total vascular	6
Neurogenic origin	
Neuroma facial nerve	1
Neurofibroma	2
Meningioma	1
Total neurogenic	4
Bone and joint origin	
Ameloblastoma	1
Vilonodular synovial sarcoma	1
Osteochondroma	2
Aneurysmal bone cyst	1
Total bone and joint	5
Total somatic tumors	44
Total lymph node tumors	
Total tumors of nonsalivary origin	98

The most common lesions that may simulate parotid neoplasms are lymph node abnormalities. When these are solitary, the distinction is often not possible. The involved node may be anywhere within or adjacent to the gland, and is often painless, firm and mobile. Generalized lymphadenopathy, previous neoplasm of the cheek, scalp or ear, infection of the adjacent skin or mucosa suggest the proper diagnosis. Often, more than one lymph node is involved; such multicentric lymphadenopathy must be distinguished from Warthin's tumors (frequently multiple) and benign lymphoepithelial disease.

Inflammatory and obstructive lesions of the parotid gland are usually easily differentiated from neoplasms. Generally there is a history of acute onset accompanied by pain and occasionally fever. In contrast to the submandibular gland, calculi are rarely the cause of obstruction of the parotid duct. In sialadenitis the entire gland is diffusely enlarged, tense and often tender. Pressure on the gland may fail to produce salivary flow from the duct orifice. Rarely, localized obstruction of a duct produces cystic dilatation that is discrete, solitary and clinically indistinguishable from a neoplasm.

Nonmalignant infiltration of the parotid by lymphocytes may result in diffuse or localized enlargement of the salivary gland and simulate a neoplasm. Originally designated as Mikulicz3s disease, this condition has been shown to be part of Sjögren's syndrome, the result of an autoimmune process often accompanied by rheumatoid arthritis, purpura, dry skin, splenomegaly, and lacrimal gland enlargement. The histologic criteria for the diagnosis of Mikulicz-Sjögren's disease were established by Morgan and Castleman in 1953.

Localized lymphoid aggregates containing mixtures of epithelium and myoepithelium clinically resemble true tumors and have been labelled adenolymphoma. Godwin stressed their benign nature and coined the name "benign lymphoepithelial lesion". Diagnosis can often be

made by study of a small biopsy sample taken from gland-bearing mucosa of the hard palate or the lip.

Lesions of the mandible or of the masseter muscle are immobile. The consistency and radiographic appearance will define osseous neoplasms and differentiate them from salivary gland tumors. In 25 cases branchial cysts have been reported within the parotid gland; such cysts arise from the first branchial cleft.

Neurilemmoma arising from the facial nerve as it courses through the parotid gland may present as an intraparotid mass. There is no facial nerve dysfunction noted preoperatively and the diagnosis is made at operation. Eleven cases were reprted in the literature up to 1972 and we have operated upon one such patient. None of the reported cases were associated with Von Recklinghausen's disease. The tumor is benign and every effort should be made to enucleate the lesion and preserve the 7th nerve.

In adults, lipomas are the most frequently encountered connective tissue tumors inthe parotid region. We found 21 cases in a total of 693 parotidectomies.

Many authors state that the most common parotid tumor in children is the hemangioma. Since it does not originate from glandular tissue, it is not truly a parotid tumor, but more likely represents a vascular hamartoma.

Primary tumors of the submandibular salivary gland must be differentiated from lesions of submandibular lymph nodes (inflammation, lymphoma, metastatic carcinoma), tumors of somatic origin (lipoma, fibroma, neurogenic tumors, vascular tumors) and diffuse enlargement of the submandibular gland. The latter is nearly always due to calculous obstruction of the excretory duct. Occlusal or oblique radiographs are diagnostic in cases of calculous obstruction. We have not found sialography necessary for diagnosis. Bilateral diffuse enlargement is sometimes noted in chronic alcoholics, diabetics, and those with high serum triglyceride levels.

Cystic lesions in the submandibular area may be difficult to differentiate from salivary gland neoplasms. The most common are dermoid cyst, cystic hygroma and "plunging" ranula.

Minor salivary gland tumors must be distinguished from inflammatory lesions of minor salivary glands, mucoceles, and in the midline of the hard palate, from the relatively common torus palatinus.

Diagnostic Aids in Salivary Gland Tumors

Lateral and oblique x-ray films may demonstrate opaque calculi in the parotid duct or gland. Calculi in the anterior portions of the submandibular duct can be demonstrated by intraoral occlusal radiographs. Osseous lesions are readily seen.

Sialography is often recommended and performed. Some authors attribute to sialography great success in differential diagnosis of many neoplastic and inflammatory diseases of the parotid. The limitations of the method are discussed by Yune et al. They were disappointed in their inability to distinguish benign and malignant tumors and could not

differentiate diffusely infiltrating lymphomas from chronic inflammatory disease. Unfortunately, sialography has failed to localize parotid tumors as deep or superficial in relation to the facial nerve. The usefulness of sialography is limited to the demonstration of beading and sacculation in cases of sialectasia and the demonstration of accessory ducts and parotid glandular tissue separate from the body of the parotid.

We believe that sialography of the parotid is rarely indicated, has limited diagnostic value and may cause trauma and irreparable damage to the duct. Since nearly all cases of submandibular duct obstruction are due to opaque calculi demonstrable clinically or on flat x-ray film, submandibular sialograms need never be performed.

Evaluation of salivary gland disease by *ultrasonography* proved to be disappointing. Its greatest value is to distinguish cystic from sold masses.

Computed axial tomography (CAT) is a valuable adjunct in the diagnosis and evaluation of extent of salivary gland tumors. Extension of deep parotid tumors to the nasopharynx and base of skull and the posterior and superior limits of salivary gland tumors involving the paranasal sinuses can often be demonstrated by this technique. With CAT scans, tumors arising from nerves, muscles or bone can in many instances be differentiated from those derived from parotid salivary gland.

Abramson et al in 1969 used technetium-99 scanning to differenitate the "hot" Warthin's tumors from "cold" mixed tumors and other neoplasms.

Needle aspiration biopsy has been advocated for the diagnosis of parotid gland tumors. We believe that needle biopsy should only be performed in cases of suspected inoperable carcinoma or in which there is clinical evidence of involvement of the facial nerve. In such instances, confirmation of the diagnosis is needed for proper treatment to be selected.

Treatment of Salivary Gland Neoplasms

The only curative treatment for the vast majority of salivary gland tumors is surgical extirpation. Resection of parotid gland tumors is complicated by the presence of the facial nerve within the gland. Hence, preservation of the uninvolved facial nerve is an essential feature of any surgical approach to parotid neoplasms. With the exception of Warthin's tumors, enucleation of parotid tumors is not advisable. Mixed tumors are often poorly encapsulated, and malignant tumors often invade surrounding glandular tissue; adequate margins of normal salivary tissue must be resected to reduce the chances of local recurrence.

Total resection of the submandibular gland is the preferred treatment for all submandibular neoplasms. Adequate resection of minor salivary gland tumors can be difficult. The lesions of the palate or gingiva frequently involve periosteum or bone, portions of which must be included in the surgical excision. In other areas of the oral cavity it may be difficult to obtain adequate margins.

In recent years, postoperative radiotherapy has resulted in improved survival rates. We have used it for most types of salivary cancer with good results.

Operative Technique of Parotidectomy

Objectives

The surgical treatment of tumors of the parotid gland must satisfy three basic objectives: (1) complete removal of the tumor; (2) preservation of the uninvolved facial nerve; and (3) cosmetic incision.

Complete Removal of the Tumor. In nearly all cases, the parotidectomy is performed without a histologic diagnosis. As discussed above, we do not favor needle aspiration biopsy in most cases. Incisional biopsy with frozen section adds additional risk of tumor spillage and the tissue biopsied is not always representative. The diagnosis of tumors that are clinically considered inoperable carcinoma may be confirmed by needle biopsy. In patients with facial nerve paralysis or gross involvement of the nerve or one of its main branches, incisional biopsy and frozen section to substantiate the diagnosis at operation should be performed before sacrificing the nerve.

Complete removal of the tumor is essential to prevent recurrences. The capsules of mixed tumors and most malignant tumors are often poorly formed or incomplete. Many of the tumors have pseudopod-like excrescences on the surface of the neoplasms. Earlier surgical approaches consisting of "shelling-out" of the tumors or intracapsular excision resulted in recurrence rates varying from 20% to 40% of cases. Resection of a margin of normal salivary tissue around the tumor is essential and almost always possible. Tumors lying directly on facial nerve branches, bone or pharyngeal mucosa, however, do not permit resecting an adequate margin of normal tissue beyond the tumor capsule in these areas. Some authors have advocated complete resection of parotid gland with or without sacrifice of facial nerve to assure such margins, even in benign cases. Such a radical approach evolved partly because of great disappointment in results following conservative procedures and partly because of the erroneous belief that salivary gland tumors are often multicentric in origin. For the majority of parotid tumors, whether benign or malignant, removal of the tumor with a margin of normal tissue constitutes adequate surgical treatment.

Preservation of the Uninvolved Facial Nerve. Unless involved by tumor, the facial nerve and its branches can be preserved. Complete familiarity with the surgical anatomy of the facial nerve, its variations, and its relationship to the parotid gland is essential for the surgeon who undertakes parotid gland surgery. Whether or not the parotid gland consists of a superficial and deep lobe with an isthmus is academic. During dissection it is noted that the facial nerve passes through the substance of the parotid gland, dividing within the gland into a variable number of peripheral branches. The terminal branches emerge from beneath the anterior border of the parotid gland to lie on the masseter muscle.

Preliminary isolation of the main trunk or one of the branches of the facial nerve and dissection in a plane superficial to the nerve will permit resection of that portion of the parotid lateral to the nerve (sometimes called "superficial lobe") if the tumor is located in that portion of the gland. If the neoplasm lies in the portion of the gland medial to the nerve (sometimes called "deep lobe"), the parotid gland superficial to the nerve is elevated, the nerve branches separated, and the deep portion of the gland is delivered between the nerve branches and resected with the enclosed tumor. In many instances in which the superficial

lobe is not involved it can be left attached and sutured back in plase to fill the defect after removal of the deep lobe, which results in a much better cosmetic appearance than if the entire gland is resected.

Depending on the location of the tumor and its size, the surgeon may use one of several surgical approaches to the exposure of the facial nerve. The most commonly practiced approach, popularized by Martin, is that of exposure of the main trunk of the facial nerve. The advantages cited for this technique are the following: (1) the anatomical location of the main trunk of the nerve is rather constant as it emerges from the stylomastoid foramen and passes toward the parotid gland; (2) the trunk is relatively large and can therefore be readily identified; (3) by starting posteriorly and dissecting in a peripheral direction, the branching is easily visualized and, although variable in number and position, all the branches of the nerve can be dissected and preserved; (4) surgeons who believe that the entire superficial "lobe", and often the "deep" lobe as well, must be resected to cure even benign neoplasms assert that it is more difficult to perform a radical resection if one starts the dissection from the periphery. In those patients with invasion of the nerve or one or more branches requiring resection of nerve segments, maintaining the integrity of the trunk near its emergence from the stylomastoid foramen facilitates nerve repair by direct reanastomosis or interposition of a nerve graft.

We believe that the exposure of the main trunk early in the operation is indicated for neoplasms diagnosed clinically as mixed tumors or possible carcinomas situated in the groove between the mastoid process and the ascending ramus of the mandible, those lying just below the auricle, and lesions just anterior to the tragus of the ear below the mandibular condyle. It is also the preferred technique in large tumors (more than 4 cm in diameter) or in those that are partially or completely fixed in position.

Small, mobile tumors lying on the ascending ramus of the mandible, on the lateral surface of the masseter muscle within the anterior portion of the parotid, or low in the "tail" of the parotid gland inferior to the angle of the mandible can generally be resected with an adequate margin of normal salivary glandular tissue without complete removal of the superficial "lobe" or near-total resection of the parotid gland. In such instances it is possible to identify nerve branches in the region of the tumor, starting the dissection peripherally beyond the borders of the parotid and tracing the respective branch or branches from before backward. Benign tumors other than mixed tumors, cysts, inflammatory lesions and intra- or paraglandular lymph nodes are enucleated and do not require exposure of the main trunk of the facial nerve unless they happen to be in the immediate vicinity of the nerve; under such conditions identification of facial nerve branches close to the lesion may be necessary to avoid accidental injury.

At times, very large or partially fixed tumors lying superficial or deep to the main trunk are so tightly wedged in the space between the bony walls of the parotid compartment that it is not possible to expose the main trunk of the facial nerve near the stylomastoid foramen without rupture of the tumor. If such tumors are superficial to the nerve, tracing the latter from anterior to posterior, starting at a peripheral branch is a preferable approach. Deep-seated lesions, especially those in a retromandibular or parapharyngeal location may require transection of the mandible, resection of the mastoid tip, division of the styloid process and/or

its attached ligaments, or combined bimanual intra- and extraoral manipulation to achieve delivery of the tumor into the wound and subsequent nerve dissection.

Occasionally, the size and location of a tumor is such as to demand exposure of the nerve from more than one directin to obtain maximal safety during dissection, either exposure of several branches or of both the peripheral branches and the main trunk. Recurrent tumors pose great difficulty in exposure and identification of nerve fibers because of the multiplicity of the recurrent lesions, their occurrence in aberrant sites often at a distance from the main body of the gland, and the adherence and cicatrization which often obliterate portions of the nerve. It is especially in these circumstances that familiarity and experience with the different surgical approaches to the facial nerve are important.

Finally, the accessory parotid containing well-encapsulated tumors can be adequately resected without sacrificing a major portion of the gland. The duct may be separated from the accessory gland after ligation of accessory ducts and preserved or, if it is attached to tumor, the duct may be ligated proximally and the distal portion resected with the tumor. One or more buccal branches, which are usually in close proximity to the accessory parotid and duct, can usually be dissected away and preserved intact.

Cosmetic Incision. Because of the location of parotid neoplasms about the face and upper neck, incisions must be planned to give an acceptable cosmetic result. Unless there is invasion of overlying skin, it is rarely necessary to make the incision in the cheek. In most cases a gentle S-shaped incision is made starting just anterior to the tragus of the ear, passing down in front of the lobule, thence curving posteriorly below the lobule and passing downward and anteriorly along the angle of the mandible. This permits the elevation of a skin flap anteriorly to expose the parotid fascia overlying nearly the entire parotid gland and posteriorly to expose the mastoid tip and the sternomastoid muscle. If the tumor lies further anteriorly in the gland or in an accessory parotid gland, the surgeon may use a horizontal extension into the temporal hairline.

Surgical Technique

Parotiectomy With Exposure of Main Trunk of Facial Nerve. First described by Janes, this approach was popularized by Martin. After the usual S-shaped incision is made, a skin flap is raised anteriorly to expose the facial covering of the parotid gland, and posteriorly to expose the cartilage of the auditory canal, the mastoid process and the sternomastoid muscle. The greater auricular nerve and its auricular branch are dissected out, retracted posteriorly and preserved. The facial branches of the greater auricular nerve are transected. The deep fascia is divided vertically along the anterior border of the sternomastoid muscle. A space is developed between the parotid gland anteriorly and the sternomastoid muscle, mastoid bone and auditory canal posteriorly. The space is gradually widened and deepened. Several vessels are seen to cross this area before the facial nerve is exposed. We prefer to ligate these with 3-0 or 4-0 catgut and divide them. The parotid gland is retracted anteriorly with some tension, using a McBurney (loop) retractor at first, and a Richardson (right-angle) retractor after a deeper plane has been reached.

The main trunk of the facial nerve is then sought. It generally crosses the wound from the stylomastoid foramen and enters the parotid gland at a point about 1.5 cm above and 1.0

cm deep to the tip of the mastoid process. The dissection is performed bluntly throughout, using a Halsted or "mosquito" clamp, alternately opening it in the direction of the nerve fibers and cutting intervening salivary tissue with scissors. If the space is not filled with the tumor, it is possible to cut through parotid tissue near the posterior border of the gland and to identify the nerve entering it. In the case of large tumors overlying the facial nerve, the exposure of the nerve is begun posterior to the lgand, closer to the exit of the nerve from the skull.

After the nerve has been identified, a horizontal plane of dissection is developed bluntly, using either clamp or scissors alternately opening and spreading in a plane just superficial to the facial nerve and its branches. Numerous small vessels are encountered passing between the portion of the gland lying deep to the nerve and the superficial portion. These may be controlled by cautery or by ligation with fine catgut. The posterior facial vein or one of its tributaries may cross the nerve and require ligation and division.

The facial nerve divides into two trunks, temporofacial and cervicofacial, 0.5-1.5 cm after entering the substance of the parotid. As these two divisions are followed anteriorly, they diverge around the so-called isthmus and further subdivide into 5-9 terminal branches with their variable intercommunications. The lobular structure of the parotid permits dissection with a blunt instrument passed through its tissues and spreading or cutting in a plane immediately superficial to the nerve branches. The ease with which the salivary tissue can split gave rise to the false impression that the parotid is composed of two lobes separated by a fascial plane.

Buccal branches of the nerve are usually two or more in number and arise from either of the two divisions of the facial nerve or from both, and often anastomose with each other or with other branches. There is often a buccal branch passing superficial to the parotid duct, usually crossing the duct or lying just above it. In resection of tumors that lie deep to the nerve or in the so-called isthmus, which bridges superficial and deep portions of the gland, a buccal branch may have to be divided in order to deliver such tumors without rupture. Sacrifice of a buccal branch may cause minimal distortion of the upper lip, or may result in no discernible deformity because of anastomoses of the nerve.

When the dissection proceeds a sufficient distance anteriorly beyond the neoplasm, the parotid tissue is transected so that adequate normal salivary tissue remains beyond the limits or capsule of the lesion. This margin should ideally be of 1-2 cm but often the capsule of the neoplasm may be as little as 1 mm from the underlying nerve or masseter muscle. Such small margins beyond benign encapsulated tumors apparently are sufficient to prevent recurrences.

Depending on the amount of salivary tissue resected and the location of this tissue, the parotid duct (of Stensen) may or may not need to be ligated or resected. Many surgeons routinely ligate and divide the duct. We agree with Conley that this is not always necessary. If the duct remains patent, residual parotid tissue will continue tofunction to a large degree. In such instances the transected parotid tissue will pour out variable amounts of saliva into the wound and occasionally cause a salivary fistula. We have never encountered fistulae of this kind that drained longer than a few weeks, though there are reports of fistulae persisting for months or years. Ligation of the main duct generally results in gradual diminution of glandular function with eventual atrophy of the residual gland.

Tumors with poor encapsulation or those that are suspected or proved to be malignant require more extensive parotidectomy. If the tumors are moderate or large in size, near-total resection of the gland should be performed. Adherence to or invasion of adjacent structures necessitates sacrifice of these structures in continuity with the resected gland. We do not advocate routine sacrifice of the entire facial nerve in cases of malignancy. The branch or branches involved, or the main trunk (when invaded by tumor) are sacrificed. In addition, portions of adjacent muscles (masseter, sternomastoid, pterygoids, posterior digastric), bones (mandible, mastoid) or skin of the face may have to be excised if invaded by tumor.

If a segment of the facial nerve and/or its branches is excised we perform immediate repair by primary anastomosis or interposition of a nerve graft.

Parotidectomy: Dissection Starting With Exposure of Mandibular Branch of Facial Nerve. Sistrunk first advocated dissection of the facial neve by exposing the mandibular branch as it cross the posterior facial vein, just anterior to the lower pole of the parotid gland, lying on the masseter just above the angle of the mandible. Adson, and later Bailey, exposed the mandibular branch, traced it posteriorly through the substance of the parotid gland until the main trunk of the facial nerve was identified. The dissection was then continued from the main trunk peripherally.

This technique is indicated for small tumors lying in the lower portion or the tail of the parotid, lesions overlying the mandible close to the angle, or bulky lesions filling the space between the mastoid and mandible and therefore making preliminary exposure of the main trink of the nerve difficult or impossible.

Small tumors situated in the tail of the parotid gland or in the thinned out portion of the gland overlying the masseter may be adequately resected with a margin of normal tissue by tracing the mandibular branch starting peripherally and lifting from the nerve branch and from the masseter the portion of parotid to be resected. In some instances additional exposure and tracing a buccal and the cervical branch are needed to permit adequate resection. Most of the parotid gland need not be disturbed in resecting such lesions.

Parotidectomy: Anterior Dissection With Preliminary Exposure of Peripheral Branches of the Facial Nerve. Anterior dissection of the facial nerve branches was first described by McCormack et al and later by State. It is the preferred approach to lesions anterior to the ear overlying the masseter muscle.

The usual S-shaped incision is made (sometime completed in a U-schape for anterior tumors). A skin flap is elevated anteriorly to expose the parotid gland and is dissected beyond the anterior margin of the gland. The individual branches of the facial nerve are each identified and traced from before backwards elevating the superficial portion of the parotid. When an area of salivary gland posterior to the limit of the tumor is reached, the gland is transected and the portion containing the tumor is removed.

Small tumors lying at a distance from the parotid capsule may be adequately resected while preserving the fascia, which can be resutured after removing the lesion, thus avoiding postoperative depression of the cheek.

Larger tumors may require both anterior peripheral branch exposure and main trunk exposure.

Parotidectomy: Dissection Starting With Exposure of Stensen's Duct. Ulin et al performed a large number of parotidectomies using a technique in which a skin flap is developed anteriorly to expose the gland, the duct and the peripheral branches of the nerve anterior to the parotid. The duct is constant in position, usually at a distance from the tumor lying within the parotid, and closely related to one or more prominent buccal branches of the nerve that usually cross the lateral aspect of the duct. With the dissection starting at the duct anterior to the gland, the buccal branches are traced posteriorly, the parotid gland gradually being lifted from the nerve and the masseter. As the dissection proceeds toward the auricle, other branches of the facial nerve come into view and are preserved.

This approach is ideally suited for tumors arising from or involving the accessory parotid, or tumors of the most anterior portion of the parotid gland. If the main parotid duct is not invaded by tumor it is possible to preserve it. Tributaries of the duct from accessory glands are ligated and divided.

Parotidectomy: Dissection Starting at the Zygomatic Arch. For tumors lying just below the zygomatic arch, or on the ascending ramus of the mandible below the condyle, the dissection is best started by exposure of the temporal and zygomatic branches of the facial nerve as they cross the zygoma. This technique was first described by Riessner, who demonstrated that the upper two branches of the nerve were more constant in position than other branches, were large in size at the level of the zygoma, and lay directly on the periosteum. Thus, it was not necessary to go through salivary tissue to expose the nerves. Parotid tumors do nmot occur at the level of the zygoma; usually the highest neoplasms are at least 0.5 cm below the arch and lie in very thin extensions of the parotid gland. By tracing the upper branches of the nerve through the parenchyma of the parotid, one can expose the upper division, and further posteriorly, the main trunk of the nerve, and partial or radical resection of the gland can be performed with preservation of the nerve. Riessner advocates exposure and division of the auriculotemporal nerve branches just anterior to the tragus of the ear in order to prevent postoperative fistula. We have not done this.

Because of the wide variation in size and position of salivary gland tumors, the parotid surgeon must be capable of using one or more of the different approaches to the dissection of the facial nerve - startnig at the main trunk, at one or more of the peripheral branches and dissecting towards the main trunk, or in especially difficult or recurrent tumors, more than one approach may be needed.

In operations for intraparotid cysts, lymph nodes, proved Warthin's tumors or lipomas, simple excision of the lesions may be accomplished without nerve exposure. Occasionally, tumors situated low in the tail of the parotid may be resected with a margin of normal salivary tissue without exposure of facial nerve.

Deep Lobe Tumors

Approximately 8-10% of parotid tumors occur in the portion of the gland deep to the facial nerve and/or its branches. Anatomically, the deep lobe extends medially for a variable

distance interposed between the mastoid process and mandible, and on a deeper plane, between the styloid process and attached ligaments, the digastric muscle, and the pharynx. Passing through this portion of the gland are the external carotid artery, bifurcating into its two terminal branches, and the posterior facial vein.

When tumors occur in the flattened portion of the deep lobe overlying the ascending ramus of the mandible or masseter muscle, they present in the cheek and are clinically indistinguishable from tumors superficial to the nerve. Our surgical approach to these tumors is as follows: a skin flap is raised anteriorly up to the anterior border of the parotid gland; the peripheral branches of the facial nerve are traced from before backwards, lifting the superficial lobe of parotid from the nerve and deep lobe. Sufficient dissection is completed to expose the underlying tumor and the facial nerve branches traversing its surface. The goal is to resect the tumor intact with a margin of uninvolved tissue around it on all sides. Often, the narrowest margin is between the nerve branches and the lesion. Using magnification and careful blunt dissection without pinching or lifting the nerves with hooks or sutures, the nervebranches are lifted from the deep lobe and the enclosed tumor and reflected away. With small tumors, lifting and deflecting two or three nerve branches may be sufficient. With the nerves lifted, the deep salivary tissue containing the tumor is dissected away from masseter, buccal fat or mandible and transected when adequate (from a few millimeters to a few centimeters) normal tissue is left around the neoplasm. If the duct is close or attached to the tuimor, it is ligated and divided. Unless the reflected superior lobe is involved or close to tumor, it is preserved and sutured back in place with interrupted fine catgut after resection of the deep lobe.

Most deep lobe tumors occur in the posterior portion of the gland. As these neoplasms enlarge they may progress in one of three directions: some tumors project deep to the mandible and may attain very large size without being clinically apparent in their full dimension. The tumors may continue to enlarge and remain confined within the tight space between the nerve, mastoid, styloid and the posterior margin of the mandible. The wedged-in tumor then appears fixed and the nerve at operation is stretched over the tumor with no interposed normal salivary tissue. Some lesions lie upon and sometimes partially surround the carotid artery. Removal of such lesions can be extremely difficult. After the superficial lobe has been dissected off and the nerve and its branches are exposed, the superficial parotid may either be resected, reflected superiorly, or divided transversely and by separating the two halves, allow dissection deep to the nerve. The facial nerve and branches are dissected off the deep lobe tumor, and the latter with surrounding salivary tissue is delivered either between the two major divisions (so-called isthmus) or by reflecting the entire nerve superiorly. The deep tissues are delivered inferiorly and resected by gradually dissecting away from the carotid, styloid, digastric and mastoid.

Several techniques have been described that facilitate resection of large, deep tumors. Nanson removed the styloid process. Occasionally dislocation of the mandible forward and laterally has permitted delivery of such neoplasms. Work and Cook describe a technique of transecting the mandible anterior to the angle and reapproximating it after resecting the tumor.

Deep lobe tumors may progress medially and form a dumbbell portion projecting into the pharynx. Such lesions often present as intraoral swellings located submucosally in the tonsillar, lateral pharyngeal or soft palate regions. The oral mass may be the only clinical

symptom or the tumor may be palpable externally as well, and often ballottable. These tumors should always be approached externally through a standard parotid gland surgical exposure. It is in these cases that the mandible may have to be divided to attain access to the lesion. Pressure on the oral mucosa over the tumor may cause the tumor to project into the parotid region and may facilitate surgical resection.

Very rarely, division of facial nerve brances to allow complete delivery of the tumor is necessary in benign tumors. When the tumor is malignant, it may be necessary to sacrifice the facial nerve completely. Nigro and Spiro found this to be necessary in 7 of 157 patients with deep lobe tumors. Our experience with nerve sacrifice has been 10 instances of complete resection of the nerve and 11 cases of sacrifice of one or more branches. In 5 additional patients the facial nerve or branches were reconstituted by insertion of autogenous nerve grafts.

Allen describes a technique of partial temporal bone resection in some deep parotid cancers. Hanna et al found it necessary to resect a portion of mandible or its condyle because of tumor adherence.

Extent of Resection of Parotid Tissue

The early belief that mixed tumors and some carcinomas were multicentric in origin led to the practice of radical (total) parotidectomy for the treatment of all or most parotid tumors. This belief was mostly based on the observation of multiple foci in recurrences. These are now known to be due to seeding or leaving numerous nests of cells behind at the time of the original operation. In mixed tumors and other benign neoplasms, the complete removal of tumor, even with the slimmest margin (often necessary where the facial nerve lay directly on the tumor), will effect a cure.

In the resection of malignant tumors the situation is more complex. As stated earlier, the exploration of the parotid gland is undertaken with no histologic identification of the type of neoplasm. If the tumor is clinically benign, our practice is to resect the superficial lobe around a tumor located within it, skirting the tumor capsule so that the line of resection passes through uninvolved salivary tissue at a distance from the tumor on all sides. The normal-appearing deep lobe is not resected in superficial tumor cases. When the tumor is in accessory parotid anteriorly, the bulk of normal parotid is not removed. Deep lobe tumors may be resected while leaving most of the uninvolved superficial lobe intact. If the final pathologic report proves the tumor to be carcinoma and the tumor was not entered nor its capsule visualized during the dissection, no further removal of parotid tissue is performed. During the past 10-15 years we have treated all malignant tumors of the parotid (with the exception of low-grade mucoepidermoid carcinoma) with postoperative radiation (see below). If the parotid tumor presents clinical evidence of malignancy (fixation, facial nerve palsy, involvement of cervical lymph nodes), more extensive parotidectomy is undertaken. When there is reasonable expectation that the facial nerve must be sacrificed, preliminary needle or incisional biopsy with frozen section is performed. Resection of most of the parotid gland (total removal of the parotid is probably not anatomically feasible), adherent nerve branches or the main facial nerve trunk if involved, portions of adjacent muscles, ligaments and bone (if involved) is done in continuity.

When possible, immediate nerve repair by primary reanastomosis or interposition of free nerve graft (greater auricular or sural nerve) is performed. Extensive loss of involved overlying skin may require use of free skin grafts or rotation of flaps (cutaneous or myocutaneous) for repair.

Some use supravital staining to facilitate parotid surgery. Methylene blue introduced into the duct preoperatively stains only the normal salivary gland tissues, leaving the tumors unstained. We have not used this approach.

Some surgeons advocate total parotidectomy with preservation of facial nerve for benign mixed tumors. We believe this approach is too radical. Anatomically, total removal of the parotid gland is probably not possible to achieve; the ramifications of the deeper portions of the gland along the pharyngeal wall, and trhe indistinct anterior extensions into the buccal region cannot be delineated. The risk of injury to the facial nerve is much greater if an attempt is made to extirpate the entire gland; Winsten and Ward report 20% facial nerve paralysis following total parotidectomy. The need for total parotid resection was predicated on the false hypothesis that mixed tumors were multicentric in origin and were low-grade malignancies.

Occasionally, the tumor lies directly on the facial nerve or one of its branches but does not infiltrate it. By careful dissection the nerve can be separated and preserved. Although in such areas no margin of normal salivary gland tissue beyond tumor capsule is resected, we have not encountered recurrence in such cases.

Complications of Parotid Gland Surgery

Facial Nerve Injury

Invasion of the facial nerve or one or more of its branches is a frequent finding in malignant salivary gland tumors. This is manifested usually by preoperative facial palsy - an ominous finding, signifying a poor prognosis. Nerve invasion with or without paralysis necessitates sacrifice of the involved nerves.

Accidental injury or transection of the facial nerve during parotidectomy may be prevented by careful exposure of the nerve and/or the branches in the region of the tumor to be resected. The nerve should never be manipulated unnecessarily, or lifted with hooks or sutures. Even the gentlest handling of the nerves may cause weakness or paresis that may last up to three months before recovery. Paralysis following temporary clamping, pinching or stretching of the nerves may persist for 6-12 months.

Occasionally, large tumors in the deep lobe cannot be delivered intact unless one or more branches of the facial nerve are sacrificed; in such instances we sometimes divide one or two buccal branches. If the nerve is severed, a primary suture repair should be performed. Three or four sutures of fine silk or prolene are used around the circumference. Segments of nerves resected may be replaced by primary nerve grafts, using portions of the greater auricular nerve or the sural nerve. Suture anastomosis or insertion of free autogenous grafts is generally highly successful, although recovery may require up to twelve or more months. In the interim, electrical stimulation of the facial muscles prevents atrophy.

Spontaneous recovery of partial facial paralysis has been reported. Martin and Helsper suggested that this may result from new pathways via the trigeminal nerve. It is more likely to be due to the frequent anastomoses present between peripheral branches of the facial nerve.

We have never seen involvement of the nerve by benign tumors although a few cases have been reported. In secondary operations for recurrent tumors the amount of scarring, with attachment to or complete surrounding of nerve branches may preclude preservation of intact nerves.

Frey Syndrome (Gustatory Sweating; Auriculotemporal Syndrome)

This symptom complex consists of sweating and flushing of the skin of the parotid region while eating. It occurs with variable frequency following parotidectomy. Some authors believe that it is nearly always present, but only rarely severe enough to be a major complaint. It usually appears 2-18 months (average 9 months) postoperatively. The area of the face involved may extend only a few centimeters anterior to the auricle or may include a wide zone of the face and upper neck.

Many theories have been proposed regarding its etiology. The most reasonable explanation is that it results from aberrant regeneration of parasympathetic (secretory fibers from the otic ganglion that reach the parotid gland via the auriculotemporal nerve) to reach sweat glands in the skin normally supplied by the auriculotemporal nerve (via postganglionic sympathetic fibers).

In rare instances the syndrome is very distressing and has even been confused with a parotid fistula. Numerous treatments have been unsuccessful (resecton of auriculotemporal nerve, intracranial section of glossopharyngeal nerve, excision of involved area of skin. Infratympanic section of Jacobsen's nerve (the tympanic nerve running from the 9th nerve via superficial petrosal to the otic ganglion) with or without section of chorda tympani has accorded relief in severe cases.

The incidence of the syndrome has decreased markedly in our experience since we have performed less radical parotidectomy in benign cases; we have never observed the syndrome in patients in whom the parotid fascia has been preserved and resutured beneath the skin.

Salivary Fistula

Wound seroma or drainage from the wound is common following parotidectomy. Repeated aspiration of the fluid, usually a mixture of saliva and serum, may be necessary. Unless the duct or one of its main branches has been severed, fistulae close spontaneously in a few weeks. In one patient, packing the wound for several days stopped profuse drainage from the wound; this was the single instance in which we have seen a persistent fistula.

Neuroma of Greater Auricular Nerve

Although many surgeons routinely divide the greater auricular nerve during parotidectomy, we do not think this is necessary or advisable in most instances. The resulting

numbness of the lobule of the ear is a distressing complication, especially in female patients. A more disturbing consequence of division of the nerve is the occasional development of a stump neuroma. This hard, tender, sometimes unsightly mass below the ear has caused such severe pain as to require reexcision, sometimes more than once, with mixed results.

Surgical Treatment of Submandibular Tumors

Principles

Resection of the submandibular salivary gland does not result in appreciable functional deficit. Since no important nerves or other structures pass through the gland, the extirpation should not cause any morbidity.

A variable number of lymph nodes are found adjacent to the submandibular gland, along the horizontal ramus of the mandible in relation to the facial vessels or overlying the gland. In contrast to the parotid, nodes are never intraglandular in this region.

The only important benign conditions of the submandibular glands are mixed tumors and inflammatory lesions. About 50% of tumors of the submandibular gland are malignant. It is usually not possible to distinguish benign from malignant lesions clinically. We therefore routinely resect the salivary gland and the associated lymph nodes of the submandibular region in all cases of submandibular salivary neoplasm.

Operative Technique

A transverse incision below and parallel to the horizontal ramus of the mandible is made through skin and platysma. Skin flaps are elevated to the mandible and to the hyoid bone. The mandibular branch of the facial nerve is identified and preserved. The lymph nodes along the mandible are separated from their superior attachments and left attached to the salivary gland, and both are separated from the mandible and masseter. The facial vessels are ligated and divided just below the point of crossing by the mandibular nerve.

The anterior belly of the digastric and the mylohyoid are retracted anteriorly to expose the floor of the submandibular triangle formed by the hyoglossus muscle. The hypoglossal nerve and accompanying lingual veins are left intact. The lingual nerve is identified and the rami connecting it to the submandibular ganglion are ligated and divided, freeing the salivary gland superiorly. The duct is then visualized, doubly ligated and divided. The facial artery entering the gland posterosuperiorly is ligated and divided. The anterior facial vein entering lower border of the gland is divided between ligatures, and the gland with associated lymph nodes is removed.

The platysma is approximated with 4-0 chromic sutures and the skin is closed with fine nylon sutures or staples.

Surgical Treatment of Minor Salivary Gland Tumors

Principles

Benign salivary tumors of the oral cavity are generally well circumscribed and readily excised, although in some regions (eg, palate, mandible) the margins of resection are limited.

The borders of intraoral malignant salivary tumors are difficut to determine clinically. The recent use of the CAT scan has been of great assistance. A variable amount of bone of the palate or mandible may have to be resected with overlying tumor to get beyond it.

Malignant salivary tumors of the nasal cavity and/or paranasal sinuses are usually diagnosed late in their course and often invade adjacent areas, such as the orbit, cranial cavity, or the inaccessible pterygoid fossa. The use of x-ray studies, tomography, and CAT scans is vital for proper assessment of their extent.

Operative Technique

The extirpation of oral neoplasms must be planned on an individual basis in each instance. Every effort must be made to obtain satisfactory margins of uninvolved tissue. Adherent mucosa should be resected. Bone subjacent to malignant tumors is resected. Closure in lip, buccal area, floor of mouth and tongue can generally be effected by primary suture. Defects in the palate that do not penetrate the full thickness can be left open to granulate and heal by secondary intention. Larger defects require local or transferred mucosal or skin flaps. Through-and-through palatal losses necessitate use of dental prostheses.

Paranasal tumors are treated by maxillectomy, smaller tumors transorally, and larger ones via the usual Weber-Ferguson cheek flap. As in major salivary gland tumors, we advocate postoperative radiation for all malignant tumors except low-grade mucoepidermoid carcinoma. The incidence of lymph node metastasis is low. When regional lymph nodes are involved, radical neck dissection is performed.

Role of Neck Dissection

There is difference of opinion concerning the indications for neck dissection in salivary gland carcinoma. Some advocate routine radical neck dissection for all malignant salivary tumors, while others perform the procedure only in patients with proved lymph node metastasis. According to Rankow, nodal metastasis is not seen in low-grade mucoepidermoid carcinoma, and is rare in acinic cell or intermediate-grade mucoepidermoid carcinoma. However, he finds a 30% incidence in adenoid cystic carcinoma, 40% in high-grade mucoepidermoid cancer and 15% in malignant mixed tumors.

MacComb et al reviewed the experience at MD Anderson Hospital and noted a difference in lymph node involvement depending on the site of the primary tumor. In the parotid gland group, there were 111 patients with malignant tumors. Of these, 60% had radical neck dissections; 28 had histologically positive nodes; and in 27 of 28, these lymph nodes were clinically palpable. Only one of 32 elective neck dissections revealed histologically positive nodes. Seven of 16 carcinomas of the submandibular glands had lymph

node metastasis (43.7%), while 23% of 100 patients with malignant lesions of minor salivary glands demonstrated involvement of lymph nodes. MacComb et al did not recommend elective neck dissections for parotid cancers, but did advocate them for malignant tumors of the submandibular glands.

We have seen only 13 cases of metastatic lymph node involvement among our patients with salivary gland carcinomas. We believe that radical neck dissection is indicated only when lymph node involvement is clinically evident.

Perzik et al believes that the decision as to whether or not to perform an elective neck dissection is determined by the histologic type of tumor. Neck dissection in the absence of palpable nodes is not advocated for malignant mixed tumors, mucoepidermoid carcinoma (except in the high-grade infiltrating type), acinic cell carcinoma and adenoid cystic carcinoma. Infiltrating adenocarcinoma and the rare squamous cell carcinoma have high incidence (over 50%) of nodal involvement and Perzik recommends elective neck dissection in these cases.

Frazell and Helsper advocate elective neck dissection in submandibular gland carcinomas. We agree with Schwartz that elective neck dissection in submandibular gland malignancies should be performed only when there is locally invasive and infiltrating tumor or in cases of anaplastic and squamous cell carcinoma.

Malignant tumors of minor salivary glands, especially those arising in the gingiva, floor of mouth or buccal mucosa, may necessitate mandibular resection to effect adequate resection. In such instances the oral resection is best combined with a neck dissection (commando operation), even in the absence of clinically palpable nodes. Most authors report extremely poor results regardless of treatment in patients with cervical node involvement from minor salivary tumors.

Postoperative Radiation Therapy of Malignant Salivary Gland Tumors

The dilemma faced by the parotid surgeon is that in the absence of a preoperative diagnosis, the parotid operation is exploratory and the procedure performed is often determined by the gross findings at operation. In cases where there is nerve paralysis or fixation to bone, muscle, skin or other structures by a malignant tumor, sacrifice of the involved neighboring structures is necessary. If, however, during the course of the operation the tumor is found to lie in close proximity to the facial nerve or one of its branches, the conservative operation with preservation of the nerve may result in an inadequate margin of normal tissue in cases of carcinoma. If the diagnosis of malignancy has been previously confirmed, on frozen section or needle aspiration biopsy, we excise a wider margin of normal parotid tissue with or without sacrifice of nerve segments. Often the diagnosis of carcinoma is returned one or two days postoperatively; reoperation is then hazardous and often unsatisfactory. Furthermore, the tendency of certain types of parotid carcinoma, notably the adenoid cystic carcinoma, is to infiltrate perineural spaces and extend for a distance from the apparently encapsulated tumor. Invasion of perivascular and marrow spaces with the growth not limited by tissue planes makes it impossible for the surgeon to be certain of complete resection of the cancer even when the extirpation is radical.

It is precisely in these instances, where residual malignant disease is minimal, microscopic and often unrecognized, that postoperative radiation in sufficient dosage over an adequate field is most likely to sterilize the small foci of tumor. Recurrence rates following operation alone, regardless of extent of operation, are distressingly high in the more aggressive forms of salivary gland malignancy, ranging between 24% and 38%. The treatment of locally advanced and recurrent tumors by radiation has usually been unsuccessful. Radiation has gradually become an essential adjunct to surgery in the case of nearly all malignant salivary gland tumors.

Until 15 years ago the only accepted definitive treatment of malignant tumors of salivary gland origin was surgery. Radiation therapy was used only for palliation in inoperable cases. Careful analysis of large series of cases demonstrated that long-term survival rates free of disease for most types of carcinoma were extremely poor following operation alone.

Early sporadic reports indicated that some salivary gland cancers were radiosensitive. Many authors, however, had advanced the view that malignant salivary gland tumors were radioresistant and thus they did not recommend radiation therapy. During the past 12-15 years considerable experience in the use of radiation combined with operation has demonstrated the value of this combined therapy method.

Jakobsson used preoperative radiation ranging from 1.200 to 3.500 rad in a variety of malignant salivary gland tumors. In 4 of 9 adenoid cystic carcinomas and 3 of 10 acinic cell cancers the palpable tumors disappeared clinically in 4-6 weeks, indicating high radiosensitivity. Other typrs of tumors did not respond so well, but the dosage was below 3.500 rad.

Beahrs reported postoperative local recurrence rates of 37.6% for moderately malignant and 72.5% for highly malignant tumors. Spiro noted a local recurrence rate of 27% after operation alone for all stages of cancer of the parotid gland. When broken down by histologic types, 5-year survival rates, as reported by Frazell, were as follows: malignant mixed tumor 55%; low-grade mucoepidermoid carcinoma 96%; high-grade 14%; squamous cell carcinoma 36%; adenoid cystic carcinoma 40%; acinic cell 82%; solid adenocarcinoma 48%; and undifferentiated tumors 24%.

Treatment after development of recurrence is usually ineffective. Kagan et al operated on 130 patients for malignant parotid tumors. Seventy-three (56%) of the patients developed recurrences one or more times. Of these, 33 are dead and 9 alive with disease. These authors suggest that routine postoperative radiation should be considered for all malignant salivary gland tumors to prevent local recurrences.

Fu analyzed treatment results in 100 previously untreated malignant salivary gland tumors. Although the cases in the study were not randomized, he compared patients treated by operation alone with those who had operation followed by radiation (5.000-7.000 rad). Radiotherapy was highly effective for microscopic disease and the incidence of local recurrence was 14% for patients receiving postoperative radiotherapy and 54% for those who did not. There was no significant difference in response to radiotherapy between different histologic types.

Tapley et al reviewed the experience at the MD Anderson Hospital. Of 54 parotid carcinoma patients treated by operation and radiation in whom tumor was histologically present at or near the margin of resection, only 11.5% developed recurrence within a 3-year period. Of those treated by operation alone, 36% had local recurrence. Their indications for radiation therapy are the following.

1. Recurrent disease after primary surgical treatment.

2. Unresectable tumor.

3. Irradiation after excision ni the following situations:

a. After parotidectomy for low-grade tumors when the surgical margins are considered questionable or inadequate.

b. After parotidectomy for high-grade tumors; in these tumors surgically adequate margins do not necessarily prevent frequent local recurrence.

c. After complete removal of recurrent tumors of all degrees of malignancy. The tumor dose advocated was 5.000 rad in 5 weeks for low-grade cancers or when treating subclinical disease (ie, after histologic confirmation of complete resection of tumor), or 5.500-6.000 rad in 5.5-6 weeks for lesions of high-grade malignancy or with definite residual disease.

At the MD Anderson Hospital, the ipsilateral aspect of the neck is also irradiated prophylactically. Only 2 patients of 48 so treated has recurrence in the irradiated field, whereas 6 patients not receiving irradiation ipsilaterally developed recurrence in the area.

Elkon reviewed a series of 52 patients with malignant salivary gland tumors; 17 patients were given early postoperative radiation therapy for microscopic residual disease or were assessed to be at high risk of local recurrence. Sixteen (94%) were free of local or regional disease 2-14 years following therapy.

Robins et al treated 20 patients with early parotid cancer by parotidectomy alone; 13 remained free of recurrence (65%). Twenty-three patients were treated by parotidectomy followed by external cobalt radiation to the parotid bed; in 20 (87%), treatment was successful. They recommend postoperative radiation for all types of parotid carcinoma except low-grade mucoepidermoid carcinoma or acinic cell carcinoma. Shidnia et al studied a group of 84 patients treated in one of three ways. Operation alone was used for early lesions and 22 pof 38 patients (58%) were free of disease. Radiation alone was used for advanced cases and 6 of 16 (37.5%) were free of disease. When operation was combined with radiation, 21 of 30 patients (70%) were alive and free of disease 2-17 years after treatment.

Specific Tumors

Benign Tumors

Mixed Tumor (Pleomorphic Adecnoma)

The benign mixed tumor, or pleomorphic adenoma, is the most common tumor of major and minor salivary glands, and shows a slight female predilection (4:3). With the exception of certain African studies, tumors extending to the posterior pharyngeal wall area demonstrate a male predominance. In an extensive study, Rauch (as quoted by Batsakis) reviewed 4.245 mixed tumors. He found that the parotid gland accounted for 85% of these, whereas the submandibular gland and minor glands accounted for 8% and 7%, respectively. Of the intraoral mixed tumors 4% arise in the hard and soft palate.

While the mixed tumor is a benign lesion, it may nevertheless undergo malignant transformation. This usually occurs after many years of slow or intermittent growth. We are of the opinion that in this sense the term carcinoma ex mixed tumor is an appropriate one. This process is thought to occur in 2-9% of all mixed tumors of the parotid gland. This will be discussed in detail later.

While mixed tumors may occur at any age, their chief incidence is within the fifth decade. The often mentioned multicentric nature of mixed tumors is in fact rather infrequent, ie, 0.5% of parotid mixed tumors. Bilateral mixed tumors are extremely rare. We have encountered only one case out of 404 benign mixed tumors. Tumors recurring after operation frequently show separate areas of recurrence.

Very slow growth characterized the mixed tumor, although sudden enlargement after a long period of quiescence is possible. At times, mixed tumors may increase in size in their early phase of development and remain unchanged thereafter.

The mixed tumor that arises within the parotid gland is usually a painless, nontender, slow-growing mass located either below or anterior to the ear. It may be found on the cheek from the region of the tragus of the ear nearly to the oral commissure, but always below the zygoma. The tumor is frequently located below the lobule of the ear, posterior to the mandible. Some tumors are grooved by the ramus of the mandible, and long-standing neoplasms may even cause pressure atrophy of the mandibular ramus. When situated in the tail of the parotid, the tumor may be at a distance below the angle of the jaw, anterior to the sternomastoid muscle.

About 10% of parotid mixed tumors take origin from the deep portion of the gland and may erode the mandible by pressure, or extend through the narrow gap between the mandible and the styloid process and stylomandibular ligament to enter the parapharyngeal space and exit in the pharynx or soft palate. These rare dumbbell tumors may obstruct the nasal choanae and/or eustachian tubes.

Mixed tumors of the oral cavity constitute more than 50% of all intraoral minor salivary gland tumors. In most areas they are mobile, except in the hard palate. The palate is the most common site, followed by the upper lip and buccal mucosa. They are rarely found

in the midline. They tend to be round, firm, nontender, and nonulcerated. Intraoral mixed tumors lack a well-defined capsule. Nevertheless, recurrences are infrequent. Eneroth reported 7 recurrences in a series of 88 palatal adenomas.

Mixed tumors of the submandibular gland present as discrete masses in that organ. Clinically they cannot be distinguished from malignant salivary gland tumors or from enlarged lymph nodes. Although mixed tumors of the submandibular glands have less well-developed capsules than those occurring in the parotid gland, recurrence occurs less commonly after removal of submandibular tumors than parotid tumors. This is readily explained by the adequacy of resection, since the surgeon is free from the concern for the facial nerve that complicates parotidectomy.

Mixed tumors range in size from a few millimeters to several centimeters in diameter. A few attain giant proportions. The shape varies from globular to lobulated or irregular. The tumor is enclosed within a connective tissue capsule, variable in thickness, and often incomplete. In areas where the capsule is deficient, neoplastic tissue lies directly in contact with adjoining salivary tissue. On section, islands of neoplasm are found within the fibrous capsule, or even appear as satellite nodules at a variable distance from the main tumor mass. Serial sections demonstrate that these satellites are in fact outgrowths, or pseudopods, continuous with the tumor, which appear separate only by an accident in sectioning.

The mixed tumor is usually firm to cartilaginous in consistency. Small tumors are mobile, while larger ones are more nodular and less movable. Deep lobe tumors are more fixed, due to the presence of the overlying nerve and branches stretched over the tumor, and because the deeper portions of such lesions may be medial to the mandible or may extend to the parapharyngeal region.

Local recurrences after removal of parotid mixed tumors were frequently reported in early studies. These resulted from inadequate removal of tumors, generally by enucleation. Residual tumor foci may persist in the form of microscopic pseudopods, or iatrogenic implants due to rupture of the capsule and spillage. Tumor recurrences tend to be multiple, and may be widely scattered, often adherent to important structures, such as nerve branches, making secondary operations very hazardous. Mixed tumors that are completely removed (ie, with a margin of normal tissue) do not recur.

Three cases of partial or complete facial paralysis have been reported due to benign mixed tumors of the parotid. Nussbaum reported a case of facial spasm associated with a mixed tumor; the spasm was relieved by resection of the tumor.

From a histomorphological standpoint, the benign mixed tumor is characterized by extreme variation from one case to another as well as within different parts of the same lesion. Related to this morphological complexity and diversity is the role of the myoepithelial cell. Assuming a facultative role resulting from its interaction with cellular elements of ductal reserve cell origin, the myoepithelial cell is thought to participate in the production of various sorts of background stromal structure, including mucoid, chondroid, osseous and myxoid material. The ratio and relationship between ductal and myoepithelial elements as well as their degree of differentiation contribute to morphological diversity and structural variation. Foote and Frazell categorized their important series of mixed tumors as extremely cellular,

predominantly cellular, and equally myxoid and cellular in 12, 22 and 36% of cases, respectively. Less cellular, more myxoid areas demonstrate a high proportion of spindle-shaped cells, whose epithelial nature is confirmed by ultrastructural examination. In a detailed in vivo and in vitro histochemical and ultrastructural study, Takeguchi et al noted two types of mixed tumors with varying cell types and histochemical features. Tumors of spindle cell predominance contained an acidic glycosaminoglycan stromal product composed of chondroitin 4 and 6 sulfates, hyaluronic acid and heparin sulfate. The second type of tumor was composed chiefly of ductal type cells with no mucinous areas and little intercellular substance.

Examples of salivary gland tumors composed nearly totally of myoepithelial cells have recently been reported. The myoepithelial cells may assume a spindle cell outline, as reported by Luna et al, or a plasmacytoid appearance with eccentric nucleus. The latter has recently been termed a "hyaline cewll", with the suggestion that this is a modified myoepithelial cell. Whether it is appropriate or necessary to use the term myoepithelioma for this variant of the mixed tumor is a point for future discourse. However, it does serve to underscore the extreme instances where this particular cell is the exclusive or nearly exclusive neoplastic element of a salivary gland tumor. Salivary tumors that are, on the other hand, composed of only ductal elements with little or no stromal background, have been considered cellular mixed tumors or, more appropriately, monomorphic adenomas. Separation of this variant from mixed tumors into the monomorphic adenoma group has provided a sense of order and understanding of salivary adenomas. Indeed, it is the feeling of Batsakis et al that the natural biologic tendency of the group of monomorphic adenoma is toward the mixed tumor.

Finally, we do not wish to create the impression that the myoepithelial cell is present only within the mixed tumor. As outlined by Hubner et al, this cell is also thought to participate in the development of many other salivary tumors, including adenoid cystic carcinomas and duct carcinomas. The presence and active participation of this cell in the histogenesis of the mixed tumor, however, must be appreciated since it does serve to explain the extreme variability in histomorphology.

Recurrent Benign Mixed Tumor

Prior to the popularization of facial nerve dissection and wide parotid resection following the report of Bailey, the incidence of recurrence of mixed tumors was extremely high, prompting early investigators to consider the mixed tumor as a malignant or semimalignant lesion. Also, because of these high recurrences rates, many surgeons used to believe that mixed tumors were multicentric in origin. Careful dissection of apparently multifocal tumors and serial sections revealed that the multiple foci were indeed artifacts, and that satellite nodules seemed independent only because of the plane of sectioning, while in fact they were actually protrusions attached to the main tumor. Enucleation or local excision of parotid mixed tumors withour margins of normal salivary tissue resulted in recurrence rates varying from 10% to 40%.

Local recurrence is infrequent following resection of submandibular mixed tumors; margins are adequate, since there is no facial nerve problem and since the entire gland is removed. Mixed tumors of minor salivary glands recur in about 10% of cases. The most

common site of recurrence is in the hard palate. Only rarely are multiple mixed tumors of true primary multicentric origin reported.

Recurrent mixed tumors are usually multiple and often are widely distributed in the area of previous operation. They often occur in association with the surgical scar or are attached to it. They are usually discrete and separate from each other and vary in size, some foci being minute. The incidence of recurrence is greater in cases that had needle aspiration biopsy (due to rupture of the capsule). Fracture of the tumor and spillage during operation may deposit fragments of tumor within the wound; simple irrigation of the wound prior to closure may prevent clinical recurrence. The frequency of recurrence seems to be independent of the histologic appearance, completeness of capsule, types of cells, and degree of cellularity. Batsakis believes, as we do, that adequacy of treatment is the prime determinant of nonrecurrence.

Recurrences grow very slowly, much as do primary tumors. They become apparent clinically after intervals of a few to many years, but most appear within 2 to 7 years. A recurrent tumor may appear solitary, but microscopically is usually multinodular. Multiple recurrences are common; in one of our patients the tumor recurred seven times after the primary excision, which had been performed at another institution. In most instances the recurrent tumor maintains the original histology; however, with each subsequent recurrence there is increased likelihood of malignant transformation.

Operation for recurrent mixed tumor of the parotid gland can be extremely difficult. As much parotid tissue should be resected as possible in order to assure removal of multiple microscopic foci. The scar of previous operation should be excised because it often contains tumor nodules. The risk of facial injury in secondary operations is great. Scar tissue often cannot be distinguished from nerve fibers, even with the use of microscopy. The nerve may be adherent to or surrounded by tumor, necessitating resection of nerve segments with anastomosis of cut ends, or nerve graft.

Monomorphic Adenoma

At one time the class of salivary tumors we currently term monomorphic adenomas was included within the nosologic umbrella of the mixed tumor or the so-called cellular mixed tumor. Separation of monomorphic adenoma was initiated by Kleinsasser and Klein. Subsequently numerous single cases or series have been reported with an attendant amount of nosologic liberalism and, in some cases, confusion. An expansion of the WHO classification by Seifert and Schulz with a more recent classification scheme by Batsakis et al is based on a histogenic concept which appropriately places a variety of cellular and architectural monomorphic lesions.

Most common among the monomorphic adenomas is the basal cell or basaloid group of lesions. Except for rare instances, the parotid gland is the most frequent site of involvement. They usually are slow growing, solitary and evolve asymptomatically over several years.

Basaloid adenomas comprise the majority of monomoprhic adenomas with three basic subtypes: canalicular, solid and trabecular-tubular. As a general statement, it may be said that,

in contrast to the mixed tumor, stromal differentiation or metaplasia is sparse or absent, with little or no myoepithelial cell component. The canalicular group generally exhibitis the greatest amount of interepithelial stroma, although the trabecular-tubular variant will often exhibit generous amounts of stroma. Encapsulation is usually present in varying degrees.

An interesting subtype of monomorphic adenoma is the *membranous adenoma*, characterized by prominent amounts of basement membrane material between tumor cells and stroma and around blood vessels within the tumor. Additionally, aggregations of pink hyaline intercellular material are often noted amongst epithelial cells. Headington et al compare this form of monomorphic adenoma, both histochemically and structurally, to the dermal cylindroma. It has been suggested by this group that the simultaneous occurrence of this salivary tumor with dermal cylindroma and trichoepithelioma may result from the action of a single pleiotropic gene upon similar stem cell groups.

The behavior of a monomorphic adenoma, if properly treated, may be considered that of a benign, nonrecurrent lesion. As with the mixed tumor, in case of inadequate removal a multifocal recurrence pattern may be noted.

Finally, the possible relationship between certain monomorphic adenomas and the mixed tumor remains to be clearly established. If such an hypothesis is an accurate one it appears likely that duct adenomas and some basaloid adenomas may represent stages in evolution to the mixed tumor.

Warthin's Tumor (Papillary Cystadenoma Lymphomatosum; Adenolymphoma)

First defined and separated in 1910 by Albrecht and Arzt, the papillary cystadenoma lymphomatosum was initially reported in the English literature by Warthin in 1929. This tumor nearly always occurs in the parotid gland, accounts for approximately 3-17% of parotid tumors and is the second most common benign salivary tumor. It is most often found in the inferior portion of the parotid gland. Rare reports of Warthin's tumor arising in the submandibular gland can be accounted for by the close proximity of the tail of the parotid to this gland, as emphasized by Batsakis. Rarely, one may encounter an example of this lesion arising in minor salivary glands of the oral cavity, larynx, nasal cavity and lacrimal caruncle. In these locations the tumor often lacks the characteristic lymphocytic component as well as the capsular characteristics of the parotid neoplasm. In this case the term papillary cystadenoma has been used, indicating absence of the lymphoid component. A review of the literature by Baden revealed a total of 19 acceptable cases of intraoral papillary cystadenoma lymphomatosum.

While found in all age groups, most Warthin's tumors occur in the fifth or sixth decade. A distinct male predilection of up to five times has been noted, nearly exclusively in whites. Of great interest is the occurrence of bilateral lesions and simultaneous unilateral multifocal lesions. Kavka's review of the literature lists 21 bilateral examples and only 4 cases of simultaneous bilateral tumors. In our own experience of 79 cases there were 13 instances of bilateral tumors (16.4%).

The clinical picture is that of a smooth, painless, relatively soft and sometimes fluctuant mass located in the lower portion of the parotid, often at the tail of the gland or

even below it, along the anterior margin of the sternomastoid muscle. It is frequently mistaken for a branchial cyst, an inflamed lymph node or a cervical abscess. The shape is elliptical and lobulation is rare, unlike the mixed tumor. The tumor grows rather slowly and may attain a size of 4 or 5 cm in diameter, apparently ceasing growing subsequently. Patients may give a history of a few months to many years duration before seeking medical advice. On rare occasions, supervening infection causes pain and possibly fever. In a few instances needle aspiration has been performed because of the diagnosis of possible abscess and a characteristic thick milky fluid obtained.

The differential diagnosis is from other parotid tumors, branchial cysts, lymph node enlargement, and other benign tumors. The inferior position within the tail of the parotid, the boggy, almost fluctuant consistency, and the long history of a painless mass in a male patient usually approximately 60 years old makes the clinical diagnosis likely. The only valuable additional diagnostic test is one we report, showing increased uptake in the Warthin tumor by technetium-99m scintiscanning.

The tumor is well encapsulated and, if the diagnosis has been made, it may be shelled out without a margin of normal salivary tissue. When exposed at operation, it possesses a characteristic smooth, lymphoid appearance with minute white specks visible through the surface. They usually lie posterior to the mandible, may be deep to it and dumbbell-shaped. Multiple tumors are not connected. If the lesion reappears at some interval following removal, it is generally thought to be a new neoplasm rather than recurrence.

Origin of Warthin's tumor within the parotid gland is related to the developmental sequence and interrelationship between parotid parenchymal elements and lymphoid tissue. Due to the lack of a definitive parotid capsule early in development, lymph nodes may be entrapped within the developing salivary gland, a capsule forming later during development. As a result, proliferating ductal and acinar elements may become included within the lymphoid tissue. Within this context a transition from normal ductal epithelium to tumor epithelium has been noted. An attractive alternative to the developmental entrapment theory is that of Allegra, who offers the possibility that the lymphocytic component represents an immune or hypersensitivity reaction toward the epithelial portion of the tumor. Attempts to identify the lymphocyte subpopulations within this tumor support the concept that the lymphoid component is residual or preexisting, and reactive in nature.

Microscopically, broad to blunted papillary processes covered by a double layer of epithelium extend into a cystic lumen which at times may be quite limited in extent. The epithelium is essentially oncocytic, with a tall columnar peripheral layer containing eosinophilic, finely granular cytoplasm and luminally oriented nuclei. An inner layer consists of cells that are smaller, cuboidal to polygonal in shape, with larger nuclei that contain delicately distributed chromatin. Occasionally, clear cells containing mucin may be scattered within the epithelium. Also noted is a cell population within the outer layer demonstrating pyknotic nuclei and deeply eosinophilic cytoplasm. When viewed ultrastructurally these cells are noted to be involuting and in the process of being shed into the cyst lumen.

Invested by the epithelial component and separated from it by a delicate basement mebrane is the lymphoid component or stroma. Germinal centers are often seen with a

surrounding well-delineated paracortical reactive zone of lymphocytes that are thought to be B-lymphocytes.

The contents of the cystic space usually are mucoid in consistency and brown in color, the pigment originating from the breakdown of the desquamated epithelial cells. This pigment is closest to ceroid pigment in nature.

Electron microscopic examination of the cytoplasm of the epithelial cell component reveals the presence of densely packed mitochondria. Many of these mitochondria are abnormal size and shape. Additionally, the internal arrangement of cristae is altered, and they are increased in number. Eosinophilic cytoplasmic granularity by light microscopy can be directly correlated to the distribution and number of these aberrant mitochondria. Tandler has reported the presence of occasional ciliated elements, lysosomes and crystalloids within these oncocytic cells.

In extremely rare cases, malignant transformation of Warthin's tumor may occur. Earlier reports of such have largely been discounted by Dobrossy et al, who themselves describe a case in which so-called mucinously transformed anaplastic cells were noted in a recurrence site of a previously benign Warthin's tumor. More recently Kessler and her colleagues reported a poorly differentiated carcinoma, originating from a Warthin's tumor, which had metastasized from the parotid gland to a cervical lymph node. A single instance of a mucoepidermoid carcinoma supervening in a Warthin's tumor has been reported, while epidermoid carcinoma has also been noted in another case report. To our knowledge no acceptable examples of malignant lymphocytic transformation within this lesion have been reported.

Oncocytoma

The oncocytoma and the closely related condition of oncocytosis represent lesions that account for 1% or less of salivary tumors. The vast majority occur within the parotid gland in individuals over 50 years of age. The question of whether the entity of oncocytoma represents a true neoplasm or a nodular hyperplastic condition has been addressed by Blanck et al. In some instances bilateral occurrences may be noted, while in individual glands (most often the parotid) multinodular patterns of growth may be seen (oncocytosis). The neoplastic character of the oncocytoma has been discussed by Berkheiser and Clough. Several histopathologic features lend support to such a claim in spite of the lack of a complete capsule and the absence of ducts or duct remnants within some lesions.

The histogenesis of the oncocytes and oncocytoma remains unclear. Hamperl believes the oncocyte to represent a mild degenerative or regressive cell with loss of organ-specific differentiation and in effect a "burned out" or effete cell. This concept is weakened, however, by the fact that these tumors are capable of accumulating sodium pertechnetate ^{99m}Tc and thus appear "hot" on scanning examination. More likely is the concept that the oncocytoma and the related condition known as oncocytosis develop from reserve cells of either excretory or intercalated ducts.

The oncocytoma is almost always characterized by a benign course with a slow growth rate, similar to that of the mixed tumor. When judging the malignancy of an oncocytoma,

acceptable criteria must include the presence of distant metastases, regional lymph node involvement, invasion of vascular, neural or lymphatic elements and malignant cytologic features with local invasion and destruction. It must be mentioned, however, that some authorities such as Johns et al feel that distinction between benign and malignant variants is not possible solely by microscopic examination.

Microscopically the oncocytic cells are characterized as swollen and eosinophilic with granular cytoplasm. Cellular outline is usually polyhedral, with single, centrally located dark nuclei.

An unequivocal diagnosis may be afforded with the aid of ultrastructural studies by the demonstration of abundant numbers of mitochondria within the cytoplasm of the tumor cells. Commonly, these mitochondria appear abnormal with large number of cristae or an unusual outline.

Benign oncocytic lesions of the parotid are treated best by superficial parotidectomy. In the case of malignant oncocytomas, some advocate removal of local regional lymph nodes in addition to the superficial parotidectomy. In minor salivary glands, removal of the benign tumor with a margin of normal tissue is adequate treatment.

Although long-term follow-up statistics are not readily available, it appears that the 5-year survival rate is good. In the case of malignant oncocytomas the overall behavior pattern is similar to that of the acinic cell carcinoma.

Sebaceous Neoplasms

Intrasalivary sebaceous gland elements were described by Hartz as developing from intralobular ducts. Intraparotid sebaceous glands may be seen adjacent to reactive lymph nodes. An overview of sebaceous cell lesions of the head and neck was published by Batsakis et al with 3 cases of sebaceous gland neoplasia arising within the parotid gland and one from the paraparotid region. Sebaceous elements within the parotid gland may be seen in several disease states. These include normal variants of intrasalivary inclusions, accompanying or adjacent to salivary neoplasms, sebaceous lymphadenomas, sebaceous carcinomas and sebaceous adenomas.

While sebaceous gland accompaniment to salivary tumors is noted to occur in less than 20% of cases, the sebaceous lymphadenoma, sebaceous carcinoma and sebaceous adenoma, in decreasing order of frequency, are far less common. Indeed, the question as to whether the sebaceous adenoma actually represents hyperplasia rather than neoplasia is a legitimate one.

Sebaceous adenomas are composed of well-differentiated lobular arrangements of sebaceous elements with well-delineated margins or encapsulation. The rounded or lobular aggregations of sebaceous glands are located within a mature fibrous connective tissue matrix. On occasion it is possible to see sebaceous elements arising from salivary ductal epithelium.

More common than the sebaceous adenoma, but still considered rare, is the sebaceous lymphadenoma. Since McGavran et al reported two cases within the parotid, approximately 12 cases have been noted in the world literature with patient age ranging from the third to

eighth decades. A distinct sex and race bias is evident, women and whites forming a substantial majority. Nearly all are located in the parotid gland. Histogenetically, the origin of this lesion and Warthin's tumor are similar, entrapment of sebaceous elements within the parotid or paraparotid lymph nodes being the origin of the sebaceous parotid tumors.

Malignant Tumors

Malignant Mixed Tumor

In early reports, all mixed tumors were considered as malignant. This was based on the frequent rare of recurrence after initial surgical treatment, the sudden appearance of a rapidly growing, metastasizing tumor after many years of quiescence, and the occasional finding of a metastatic focus although histologically it had the appearance of a perfectly benign mixed tumor.

In several large series of major salivary gland neoplasms the incidence of malignant mixed tumors varies from less than 2% to 10%. Although group variation must be considered a prime reason for this variability of incidence, another possibility must be considered; namely, that two very different sorts of lesions were evaluated. By this we mean the carcinoma arising in a previously benign mixed tumor, usually of long duration prior to the development of malignant transformation and the "true" malignant mixed tumor. The latter is considered very rare and is thought to exist in two forms. One type, as recently reported by Chen, demonstrates identical appearing areas of histologically benign mixed tumor at the primary and metastatic sites. The second type of malignant mixed tumor is histologically heterologous, with areas of obvious carcinoma and mesenchymal malignancy (essentially a carcinosarcoma). Metastases in this variant contain elements of both cell lines with an overall resemblance to the primary tumor.

The more common of the two malignancies is the carcinoma ex mixed tumor. This tumor is more frequently encountered in women; a recent study indicates a 3:1 female predilection. It is usually found in patients approximately 10-20 years older than those with benign mixed tumor. It has been demonstrated that the incidence of malignancy developing in mixed tumors increases significantly with time, up to a 9% incidence of transformation in benign tumors existing over 15 years. Clinical history and presentation is often that of a slowly growing or apparently unchanged salivary gland tumor present for 10-15 years or longer, which suddenly grows at a rapid rate, sometimes producing pain and occasionally involvement of the facial nerve. Rarely, the history is short, suggesting that the malignancy has been present ab initio with no benign epithelial features recognizable. In recurrent or persistent mixed tumors, Slaughter et al noted the incidence of malignancy to increase with each recurrence. Thackray and Lucas estimate that, if left untreated, about 25% of benign mixed tumors would become malignant. The probability of such a malignant change may be increased with previous radiotherapy to the area.

The diagnosis of carcinoma arising in a benign mixed tumor relies on the presence of extension and infiltration into the adjacent tissues. The most common type of carcinoma to develop within a mixed tumor is adenocarcinoma, undifferentiated carcinoma being the second most common. Squamous cell carcinoma and mucoepidermoid carcinoma are reported less often, while adenoid cystic carcinoma ex mixed tumor is rare.

Microscopic features of a putative mixed tumor that may lead a pathologist to question its benignity include small zones of necrosis, sometimes associated with a dystrophic type of mineralization. Infiltration of epithelial cords into a well-hyalinized stromal component is another criterion of malignancy. These cords as well as other areas of epithelial proliferation demonstrate the usual cytologic features of malignancy such as nuclear pleomorphism, nuclear atypia, increased mitotic activity and inversion of nuclear-cytoplasmic ration. Although many growth patterns of the malignant component may exist, multiple areas of solid lobular growth and infiltrative destructive growth are believed to be the most reliable criteria of malignancy. More obvious structural features of malignancy include vasclar, lymphatic and/or perineural invasion, and some studies report the latter finding to range from 14% to 50%.

We agree with those investigators who advocate radical parotidectomy as the preferred treatment for carcinoma ex mixed tumor with or without a neck dissection. Others advocate total parotidectomy or minimally a wide margin of uninvolved salivary tissue. Spiro et al, on the other hand, use a conservative approach; 66% of their cases involving the parotid gland were treated by subtotal parotidectomy. Of these, facial nerve function was preserved in 46%; radical neck dissection was performed in less than one fourth of their cases. Most treatment centers have been using postoperative radiotherapy with encouraging results as compared to surgery alone. Radiotherapy alone offers little hope of cure or long-term control of disease.

Metastatic lesions and local recurrences are frequent, ranging from 38% to 71%. Favored sites of metastasis beyond regional lymph nodes include lung, brain and bone. Such rates of recurrence and metastasis result in a poor overall prognosis. While the study of LiVolsi and Perzion shows a 35% rate of survival in patients followed five or more years, others report long-term survival rates to range from 19% at 15 years to 0% at 20 years.

Mucoepidermoid Carcinoma

In 1945, Stewart et al separated the mucoepidermoid "tumor" from the mixed tumor group. Initially they distinguished "benign" and "malignant" variants, but after noting metastases in some cases of the so-called benign tumors they reclassified all of them as malignant. This view is shared by Batsakis, Eneroth, and ourselvers. Other authors continue to classify mucoepidermoid lesions as benign or malignant-behaving neoplasms and prefer to designate the entire group as "mucoepidermoid tumors".

Mucoepidermoid carcinomas are the most common malignant tumors of salivary origin, comprising between 6% and 9% of all salivary gland tumors. In Eneroth's large series of malignant salivary tumors, mucoepidermoid carcinoma comprised 23% of parotid malignancies; 9.5% in the submandibular gland and 35% in the palate.

The clinical picture depends on the degree of infiltration, histologic grade of the tumor and the stage or extent of the disease. Low-grade tumors are clinically indistinguishable from mixed tumors. They are firm, lobulated, movable and asymptomatic. The duration of symptoms averages 6.4 years. High-grade tumors may be fixed to neighboring tissues and produce pain or facial nerve paralysis. The tumors are slightly more common in women. Their size is variable, but rarely larger than 3 cm for low-grade lesions. The less malignant forms often have cystic components. In the palate, the high-grade tumors often appear ulcerated or invade underlying palatal or alveolar bone, often causing loosening of a tooth.

Spiro et al made a comprehensive study of 367 cases of mucoepidermoid carcinoma. Of these, 152 were recurrent following a previous surgical procedure. Parotid and submandibular tumors that were considered low grade presented as an asymptomatic lump. Intermediate and high-grade parotid lesions presented with fixation and/or ulceration in 38% of cases and facial nerve palsy in 17%. Pain was present in 13 of 254 parotid cases and in 3 of 23 submandibular tumors. In the minor salivary glands, mucosal ulceration was frequent but bony involvement of the jaws was rare. Nearly all lesions of the antrum or nasal cavity were sizable tumors with marked bony destruction. Metastasis to lymph nodes occurred in 29% of patients. This happened more often in tumors of the submandibular gland and in high-grade tumors that presented as recurrences.

Low-grade types of mucoepidermoid carcinomas demonstrate a dual population of well-defined mucous and epidermoid cells. Architecturally, these elements, in the low-grade lesion, often demonstrate cyst formation. The caliber of such cysts or glandlike spaces may be rather large at times, whereas in other instances microcystic features may predominate. Predominant cellular features include highly differentiated mucous goblet cells and more cuboidal elements with eosinophilic to vacuolated cytoplasm. Epidermoid or squamous elements generally form the minority of the cell population, while clear cells are rare in most tumors. On occasion, however, clear cells may form a significant or near-total percentage of the lesion, producing a hypernephroma-like appearance. This is the so-called clear cell variant of mucoepidermoid carcinoma, which may at times be a diagnostic challenge to the pathologist. Little evidence of dysplasia or cellular pleomorphismmm is noted within the low-grade carcinoma. A fourth cell type, the intermediate cell, may be found within the lining cell population of the cystic lumens. Speculation is that this cell possesses the ability to differentiate toward epidermoid and mucous elements or clear cells.

Other cell types that may represent components of the mucoepidermoid carcinoma have been identified by Sikorowa; these include maternal and columnar cells. The former cell type is thought to be derived from medium-to-large caliber ductal elements. Standard mucin stains fail to stain these cells, which are considered to represent the progenitor of all other cell types in this lesion. Columnar cells, the sixth of potential cellular subpopulations, demonstrate positive staining with standard mucin stains. Mucous cells are considered to be derived from these elements.

Recurrences are frequent in mucoepidermoid carcinomas. Frazell reported that 15% of low-grade and 60% of high-grade tumors recurred. A 75% recurrence rate was reported by Stevenson and Hazard, while Jakobsson and Batsakis noted a 60% local recurrence rate. Thorvaldsson et al reported recurrence rates of 1% and 71% respectively for low-grade and high-grade tumors. Healey et al studied 60 patients with mucoepidermoid carcinoma. They noted that recurrences were related to the degree of histologic differentiation and the presence or absence of tumor along the line of surgical resection. Only 1 of 31 patients had a recurrence when no tumor was found at the line of resection. Recurrence was noted in 19 of 28 cases with tumor at the line of resection, whereas the other 9 had additional radical surgical treatment, and did not experience further recurrence. Cutaneous, osseous, pulmonary and cerebral metastases may occur. Prognosis correlates well with histologic grading, clinical stage, DNA content of the cells and type of therapy.

Low-grade tumors have an excellent prognosis, similar to that of mixed tumors. In the series reported by Spiro et al, 5-year survival rates with low-, intermediate- or high-grade tumors were 92, 63 and 27%, respectively. Five-year survival rates with clinical stage I, II and III lesions were 97, 83 and 28%, respectively.

An intermediate subgroup demonstrates a greater degree of cellularity with formation of fewer cystic spaces or gland-like structures than the low-grade malignancy. Epidermoid elements and intermediate cell components comprise most of the lesion, while well-formed mucous cysts and goblet cells occupy a less prominent histologic role. As can be anticipated, a greater degree of cellular atypia and invasiveness are evident.

The most aggressive variant, the high-grade form, displays a predominant squamous or epidermoid cell population, which exhibits a considerable degree of dysplasia, pleomorphism, mitotic activity and invasiveness. Clearly defined mucous elements are often difficult to identify, although cellular mucus may be as prominent as the squamous component. Aggregates of tumor cells form sheets and islands that may be indistinguishable from squamous cell carcinoma.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma of salivary gland origin comprises a relatively small percentage of major and minor salivary gland neoplasms, ranging in frequency from 6.5% to 10% in two large series. Although these tumors have been noted in several non-salivary gland sites, such as breasts, lacrimal glands and skin adnexal regions, the salivary glands are the most common location. Of interest is the significant proportion of these arising in minor salivary glands, often insidiously. In the series of Spiro et al, more than 70% of cases arose from minor salivary glands, while Conley and Dingman reported that the minor salivary glands accounted for 58% of these adenoid cystic carcinomas arising in the head and neck region.

Testimony to the aggressiveness of this lesion is early invasion of the facial nerve, 4% of cases presenting with facial nerve paralysis, while 18% of patients initially have pain as a clinical symptom. Bone invasion was noted in 50% of tumors involving minor glands in the study by Spiro et al.

In the same study it was shown that adenoid cystic carcinoma of the parotid gland invaded branches of the facial nerve in 16% of cases, while in the submandibular gland this phenomenon was noted in 10% of cases. Peculiar to the accepted aggressive behavior pattern is the slow growth of the lesion. This slow growth, however, must be considered along with the fact that a very invasive, infiltrative growth pattern also characterizes this tumor. These facts help explain statements made by some authors regarding the incurability of this entity or poor long-term prognosis, especially when local recurrence takes place.

Adenoid cystic carcinoma of the parotid gland is well described by Cummings. In accumulated series, facial pain was common, occurring in as many as 50% of patients. This has been attributed to perineural invasion, a frequent histologic finding. Bauer and Bauer observed that all adenoid cystic carcinomas in their series showed invasion of nerve sheaths. Twenty percent of patients developed some form of facial paralysis, which indicates a poor

prognosis. All of Eneroth's adenoid cystic carcinomas presenting with facial paralysis had a fatal outcome. In the series reported by Cummings, 8 of their 14 patients presented with facial nerve paralysis; 3 of these survived for more than five years free of disease. All had combined surgery and radiation.

From a histogenetic standpoint it appears that the terminal canaliculi or intercalated duct elements probably give rise to this tumor. Detailed structural descriptions of the adenoid cystic carcinoma are found in numerous reports. Recent ultrastructural analysis have defined the fine anatomical details of both cellular and extracellular elements of this entity and have supported the thesis that the state of cellular development or differentiation of the adenoid cystic carcinoma parallels that of the immature intercalated duct cell.

Two fundamental structural patterns are usually associated with the adenoid cystic carcinoma. In a typical lesion the so-called cribriform pattern forms a reticular network of nests, cords and strands in association with cystlike spaces. These spaces contain PAS-positive, diastases resistant material that often appears fibrillar and may be mistaken for mucin. At the ultrastructural level this material has been identified as a basal lamina material, bearing no resemblance to mucin. Other cystlike spaces may also be noted that may be appropriately termed true lumina. These true lumina are few in number when compared to the more common cribriform areas, although they are quite distinctive when viewed ultrastructurally. Sometimes in association with the cribriform pattern one may witness sharply demarcated areas of solid growth pattern with little tendency toward lumen formation. Occasionally central zones of necrosis may be present within these solid areas.

In both the cribriform and solid variants of adenoid cystic carcinoma the individual cells comprising the tumor tend to be rather small, isomorphic and monotonous in nature, with little pleomorphism or mitotic activity. Nuclei are large and quite regular in outline with fairly dense chromating aggregates. The overall basaloid appearance of the cells tends to support the intercalated duct cell as the cell of origin of this neoplasm.

From a histochemical standpoint it has been stated that different categories of mucosubstances exist within the pseudocystic spaces when compared to the so-called true ducts within the adenoid cystic carcinoma. Pseudocystic spaces, which are considered by many to be the prime structural feature of this tumor, have been shown to contain large amounts of sulfated mucopolysaccharides, while mucins within tumor ducts behave histochemically as neutral glycoproteins and sialomucins. Fine structural differences between the materials found in two types of lumen (pseudocyst vs glandular lumen) would seem to confirm the histochemical data.

There is wide variation in the treatment of adenoid cystic cancer of the parotid as advocated by different clinics. Surgery is the principal modality of treatment. Wide resection, consisting of superficial parotid lobectomy or superficial and deep lobectomy while sparing the uninvolved nerve is practiced by most authors. Some surgeons believe the facial nerve should not be spared; State recommends resection of the facial nerve only if it approximates or is invaded by the tumor.

Fu et al reported that only 3 of 10 patients with adenoid cystic carcinoma treated by operation alone achieved initial control, whereas 9 of the 10 patients who had excision plus

postoperative radiotherapy were successfully treated. Survival rates following treatment of adenoid cystic carcinomas are generally poor. Spiro reported "cure" rates 5, 10 and 15 years following initial therapy of 31, 18 and 10%, respectively. These figures are similar to those of Seaver and Kuehn. In patients with adenoid cystic carcinoma of intraoral minor salivary glands, Tarpley and Giansanti reported no survivors 20 years after initial treatment.

The value of radiotherapy in the treatment of adenoid cystic carcinoma of the parotid has been the subject of controversy. Connell et al believe it produces temporary remission without altering prognosis. Fletcher et al and Cummings recommended routine use of radiotherapy following parotidectomy and reported improved results. In our own patients we have used external cobalt radiation postoperatively for the past 15 years. Survival and recurrence rates after 5 and 10 years were similar in the irradiated and nonirradiated cases. Von Miert et al used radium implants subsequent to removal of the tumor in 6 patients and noted no recurrences.

Lymph node involvement is rare and, as pointed out by Marsh et al, the nodes are invaded by direct extension rather than via embolic route. Radical neck dissection is indicated when nodes are clinically involved. Lymph node-bearing areas adjacent to the parotid are generally included in the treatment field during radiation therapy.

The treatment of adenoid cystic carcinoma of the nasal cavity and paranasal sinuses is generally futile. Tauxe et al reported 27 cases of adenoid cystic carcinoma of the upper respiratory passages - all patients died of disease a few weeks to 15 years after treatment.

Perzin et al classified 62 cases within major and minor salivary glands according to predominant histologic pattern and found a correlation with prognosis. Recurrences occurred in 59% of those with "tubular" pattern, 89% of "cribriform" lesions and 100% of "solid" neoplasms. The importance of adequate resection is emphasied by Smith et al. None of their patients who had clear margins in surgical specimens developed subsequent distant metastasis. Local recurrences occurred up to 8 years after initial therapy and could not be successfully treated.

Acinous (Acinic) Cell Carcinoma

While acinic cell tumors were first described by Nasse, Buxton et al were the first to indicate that this group of salivary gland lesions were capable of a malignant behavior. Foote and Frazell assessed a series of 900 major salivary gland tumors in which 21 were diagnosed as acinic cell carcinoma. As with the terminology of tumor vs carcinoma in dealing with the mucoepidermoid carcinoma, some authors have confused the issue by calling all acinic cell lesions "tumors", claiming that benign and malignant variants may be recognized. The high recurrence rates and the incidence of metastases compels us to agree with Batsakis et al who believe that all acinic cell lesions should be considered carcinomas. In agreement are Abrams et al who reviewed 77 cases of acinic cell carcinoma of major salivary glands, and more recently Spiro et al who noted a 15-year survival or determinate cure rate of 55%; the latter study emphasizes the biologic potential of this lesion, especially when the primary tumor is extensive at the time of diagnosis. Because of lack of agreement regarding the malignant nature of this lesion, there are marked differences in management, ranging from very radical operation to conservative local excision.

Within the parotid gland the acinic cell carcinoma accounts for approximately 2.8% of all tumors with a range of 2.1% to 4%, while of parotid gland malignancies it represents from 7.2-19% of cases. In minor salivary glands this neoplasm is considered to be rare; only 30 cases were reported up to 1978. Of malignant salivary tumors, the acinic cell carcinoma occurs bilaterally most often, with only the Warthin's tumor occurring bilaterally more frequently. In the pediatric age group this tumor is the second most common salivary malignancy; the most common is the mucoepidermoid carcinoma. A slight female predominance is noted when surveying most large series, and the fifth decade represents the peak age of incidence, although this lesion may occur in any age group from the first through the eighth decade.

The clinical presentation of this neoplasm does not differ from that of other salivary tumors. It generally appears as a solitaly, lobulated, mobile mass ranging from a few millimeters to 3 or 4 centimeters in diameter. Growth rate is usually slow, with a history of from less than a year to 10 years or more. Occasionally a long period of slow evolution may be followed by a sudden rapid increase in size. In one series, pain, either spontaneous or upon palpation, occurred in one third of patients, while only 7% of patients in the study of Spiro et al complained of pain. In a large series reported by Abrams et al pain was present in 44% of cases. Less common than pain was the occurrence of preoperative facial nerve palsy. Most studies report a 3% incidence or less. Lymph node involvement occurs in less than 10% of patients, although Spiro et al noted a 16% rate of cervical lymph node metastases in a combined series of major and minor gland lesions. An uncommon clinical variant presents as a pure cystic lesion unlike the usual solid or microcystic tumor. Examples of the cystic form were reported by Frazell, and more recently, Hanson described two cases, calling attention to the atypical clinical and histologic features. We have treated two patients who presented with cystic lesions, in one of whom the true nature of the tumor was recognized only after the cyst recurred twice after excision. Abrams reviewed a large series of cases of acinic cell carcinoma of minor salivary glands.

Several cell types and growth patterns characterize this neoplasm. While it is believed that origin from the terminal or intercalated duct component of the ductal apparatus is most likely, others have suggested a striated duct or acinar origin. The cell type that is most striking and most numerous is the "acinic" cell with its rather granular cytoplasm. The cytoplasmic texture varies from course to fine, imparting an overall degree of basophils to the cytoplasm. Other cell types include vacuolated cells, duct cells and clear cells, as well as nonspecific glandular cells. In any given lesion one cell type may predominate and on rare occasions a nearly pure population of clear cells is found. This so-called clear cell variant, although accepted by some as an artifactual phenomenon related to degranulation of serous (acinous) cells, may represent an immature acinous cell population that has failed to reach a level of differentiation concomitant with formation of mature secretory granules. Stromal features are usually ill defined and inconspicuous. When evident, as in the papillary forms, the stroma around neoplastic elements is delicate, with sparse fibroblasts. When multinodular patterns are present, however, a more dense collagenized background may be seen, with hyalinized stroma being present in approximately 10% of cases.

A variety of overall growth patterns may be found in sampling a large number of acinic cell carcinomas. The least typical pattern may be the cystic form, with papillary intracystic projections and oncocyte-like or acidophilic cells. Most commonly observed is the

solid growth pattern composed of well-differentiated acinic cells with areas of acinar, glandlike formation. In many areas small zones of microcystic degeneration may be present, probably secondary to cell lysis. Other growth patterns include the follicular and papillary-cystic types. A true capsule is often absent, although stromal condensation is seen, with a multinodular, and on occasion, a true multifocal or even bilateral pattern (about 3% of cases).

Ultrastructurally, the acinar or serous appearance is usually quite evident in the majority of the neoplastic cell population. These cells display a luxuriant amount of granular endoplasmic reticulum and a rich concentration of secretory granules. Generally the Golgi complex is multifocal in nature where the terminal ends often seem to give rise to precursor secretory granules. Cell borders are uneven with numerous microvilli interdigitating with those from adjoining cells. Well-formed desmosomes link these cells.

The true malignant nature of acinic cell tumors can only be appreciated by studying long-term survival following treatment of this slow-growing neoplasm. Spiro reports determinate "cure" rates of 76, 63 and 55% at 5, 10 and 15 years. In an extensive review of reported series, Batsakis et al quote local recurrence rates of 10-55%, metastasis in 30-50% and death due to cancer in 12-35% of cases. Fatalities may result from local extension or distant metastases to lungs or the skeletal system, particularly the spinal column. Like Warthin's tumors, acinic cell carcinoma may arise in ductal or intraparotid inclusions in paraparotid or intraparotid lymph nodes; such lesions should not be confused with metastatic tumor.

As in other parotid tumors, the surgical approach in discrete, mobile lesions consists of subtotal resection of the gland with preservation of uninvolved facial nerve branches without prior biopsy. More extensive tumors, including those with nerve invasion, attachment to skin or bone, are treated more aggressively. If cervical lymph nodes are involved, radical neck dissection is indicated. Although primary treatment of these tumors by external radiation has not proved effective, we administer postoperative radiation in all cases. Preliminary reports indicate that the use of 5.000-6.000 rad of cobalt following surgery results in improved survival rates.

Summary of Authors' Experience

Over a period of 30 years we have performed 854 salivary gland operations. Of these, there were 693 parotid gland operations, 107 resections of submandibular salivary glands, and 54 excisions of tumors involving intraoral minor salivary glands.

Of parotid tumors operated on, 535 were located in the "superficial lobe" and 101 in the "deep lobe". Tables 11-13 summarize these parotid operations. The most common lesion encountered within the parotid gland was the benign mixed tumor, totalling 404 cases. Of these, 358 were first operated on by us; to our knowledge only two of this group had local recurrences, both of which were successfully removed. Forty-six patients had had 1-6 previous operations elsewhere.

Our experience with submandibular and minor salivary gland operations is shown in Tables 14 and 15.

Conclusions

A thorough knowledge of the pathologic features and clinical behavior of salivary gland tumors is a prerequisite for their proper management. An attempt was madwe to include more recent advances in pathogenesis and structural aspects of tumors in a rather comprehensive discussion of benign and malignant neoplasms.

Based on the location of the tumors within the parotid gland, several surgical approaches to facial nerve dissection have been used. We believe that in most instances, resection of the tumors with wide margins of normal salivary gland tissue beyond the lesions is adequate. The so-called total parotidectomy is neither necessary nor feasible.

In all malignant salivary tumors except low-grade mucoepidermoid cancers, we advocate routine postoperative irradiation.

Radical neck dissection in the management of salivary gland malignancies is generally indicated when lymph nodes are palpably enlarged or histologically proved to contain cancer. Occasionally, in highly aggressive carcinomas, elective neck dissection may be performed.

Table 11. Surgical Approaches - Parotidectomy (Authors' Experience, 1951-1980).

Main facial n. trunk (Janes, Martin)	385
Anterior approach (McCormack, State)	120
Duct exposure - for accessory parotid (Ulin)	11
Zygomatic branch (Riessner)	4
Mandibular branch (Sistrunk, Bailey)	42
Partial parotidectomy or enucleation	82
Anterior and main trunk approach	10
"Total" parotidectomy - nerve sacrificed	9
Incomplete resection	28
Biopsy only	2
Total	693

Table 12. Benign Lesions of Parotid Gland (Authors' Experience, 1951-1980)

Mixed tumor	404
Warthin's tumor (13 had 2 tumors)	79
Teratoma	1
Lymphangioma	5
Hemangioma	4
Papillary cystadenoma	4
Cyst	15
Oncocytoma	2
Lymphoepithelial lesion	14
Boeck's sarcoid	3
Basal cell adenoma	1
Lipoma	21
Tuberculosis	2
Ectasia or fibrosis	22
Total	590

Table 13. Malignant Tumors of Parotid Gland (Authors' Experience, 1951-1980)

Mucoepidermoid carcinoma	35
Log-grade21	
Intermediat7e	
High-grade	7
Acinic cell carcinoma (2 recurrent)	15
Adenoid cystic carcinoma (2 recurrent)	14
Adenocarcinoma	10
Papillary carcinoma	2
Epidermoid carcinoma	1
Adenocarcinoma ex mixed tumor	2
Anaplastic carcinoma	2
Lymphoma	15
Metastatic carcinoma	7
Epidermoid	3
Melanoma	2
Breast cancer	2
Total	103

Table 14. Submandibular Gland Operations (Authors' Experience, 1951-1980)

Benign mixed tumor (2 recurrent)	31
Malignant mixed tumor	2
Adenoid cystic carcinoma (1 recurrent)	10
Mucoepidermoid carcinoma	7
Low-grade	
Intermediate	
High-ghrade	
Adenocarcinoma	1
Carcinoma ex mixed tumor	1
Anaplastic carcinoma	1
Lymphoma	8
Chronic sialadenitis	45
Lymphoepithelial lesion	1
Total	107

Table 15. Minor Salivary Gland Operations (Authors' Experience, 1951-1980)

	Benign Mixed	Malignant Mixed	Muco Epidermoid	Adenoid Cystic	Acinic Cell	Adenoca
Palate	2	1	9	1	1	1
Lip	2		1	2		
Gingiva			4	1	1	1
Buccal mucosa	3		4	1	1	
Tongue			1	1		
Maxilla			1	5		
Sublingual			1			