SALIVARY GLAND TUMORS

By

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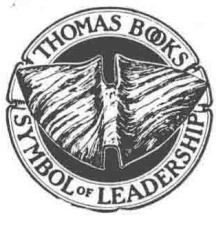

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FOREWORD

BLAND SUTTON aptly said, "Tumors of the salivary gland are a pathological puzzle and a source of unsatisfactory speculation." Theories relative to histogenesis are legion and confusing. There is no continuity of opinion among the best pathologists of the land. Physicians do not realize adequately the serious nature and the potential danger of malignancy in these tumors. There is a deep dread of injuring the facial nerve. This leads to procrastination, and there is an average duration of seven years before surgical intervention. The object of this paper is to emphasize the anatomy of this area and pathological behavior of the tumors. The conclusions drawn from this study lead to definite criteria for surgery. Principles of surgery are outlined, and the surgical technic is described in detail. Certainly, all should realize that these tumors can be removed adequately, and yet the facial nerve can, except in rare cases, be saved.

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I

HISTORY

Little was known about the glands of the body up to the middle of the seventeenth century. Niels Stensen (1638-1686), while dissecting in Amsterdam, discovered and described the duct of the parotid gland which now bears his name. Lorenz Heister (1683-1753) tells of operating on the parotid, but does not say if the nerve was injured. The first published reports of tumors of the parotid are generally credited to C. G. Siebold, in 1793, and J. P. Siebold, in 1797. Siebold's first operation was performed in 1781. Other early operators were Abernathy and Goodland, in 1815; Carmichael, 1818; Gensoul, 1824; and Lisfranc, in 1826.

In 1841, A Berand published a thesis with the first attempt at classification of these tumors. Billroth, in 1859, published some articles describing the parotid tumor so well that his intimate detail could very well be used today. Other articles of significance were written by Bruns, in 1859; Virchow, in 1863; and Minssen's comprehensive review, in 1874. Paget described these tumors occurring in the palate in 1886. Robin, in 1852; Foremegia, in 1883; and Royer, in 1889, also described tumors in the palate.

The operation was apparently performed in this country by John Warren, in 1798. This was not reported, and mention of it was made later by John Collins Warren, who also quoted Agnew as stating that McClellan of Greencastle, Pennsylvania, removed the parotid in 1805. Others who repeatedly operated on the parotid are White, of Hudson, New York, in 1808; Sweat of Maine, in 1811. The latter operated on three cases, but these were not reported until 1851, when his article appeared in the *New York Journal of Medicine,* Volume VII. Doctor John Beale Daridge performed an operation in 1823, but it was reported in a journal that lasted only one copy (*Baltimore Philosophical Journal and Review,* Volume I, Number I).

Doctor Granville Sharp Pattison, Professor of Anatomy in Jefferson, gave a speech on the subject, "Has the Parotid Gland Ever Been Extirpated?" He apparently emphatically stated that it had and that the first operation was a total parotidectomy performed on a Doctor Graham. Doctor McClellan founded Jefferson Medical College. Great credit must be given him, for he operated upon this gland 11 times with 10 recoveries. He published his results and lectured on the subject and established clearly that the operation was feasible and practical. In this way, he is often referred to as the pioneer of this type of surgery.

Progress has steadily continued until now the literature on this subject is very large. Standing out prominently on the horizon are the early writings of McFarland, Bailey, and Janes, who emphasized the importance of these tumors in our minds and made further helpful suggestions relative to surgical technique.

II

PAROTID TUMORS

HISTOGENESIS

THE ORIGIN of parotid tumors is a matter of considerable controversy. There are many theories, but none of them seem to explain all the variations seen in these tumors. Only a summary of the theories will be given here.

Billroth, Virchow, and Kaufmann, felt that they were derived from mesenchymal tissue. Kolacek, Watmann, Nasse, and Volkmann believed that the derivation was from vascular endothelium. Cohnheim, Birch-Hirschfeld, Cuneo and Veau, Fredet and Chevassu all claimed an origin from branchial clefts. Hinsberg assumed that detached or misplaced salivary gland embryonic cells were responsible for the later development of the tumor. Verneuil, Planteau and Duplay felt that the tumors developed from the adult gland tissue.

Most modern observers agree that the origin of these tumors is from embryonic epithelium in the formation of the gland, but differ in their viewpoint as to timing.

According to Hammar, the beginning of the parotid development occurs at the end of the first month (8 mm. fetus). At first there is a groove in the cheek, this deepens and sinks into the tissue of the cheek and becomes detached from the epithelium except at its very anterior end where it remains attached near the angle of the mouth, constituting the orifice of the duct. This becomes a solid cord, gradually lengthening and growing back toward the ear. The cord produces buds to form the lobules of the gland, following which the gradual canalization of this cord like structure occurs, and the development proceeds until the adult type of gland and tubes is complete. The cord has the power to keep on budding as long as it remains solid. This process is well described by Grosser.

Wood and Wilms feel that detachment of some of these cells occurs very early in the above development. Pitance suggested that some buds were broken off and detached in the later development and form the nucleus of a tumor. In any case, if tumors are developed from these early embryonal cells it would be only reasonable to expect considerable diversity of structure.

A simple adenoma may develop from the adult gland tissue either from the acini or ducts. These are very rare tumors.

Wood has suggested a teratoma as an origin of some of these complex tumors. Fry concludes that the mixed tumors are derived from the adult gland structure and from duct epithelium. The mucinous material is a secretion of the cells. At no time is true cartilage present, there is only compressed mucoid material.

Halpert is of the opinion these tumors are derived from nests of embryonic ectoderm. They occur along facial fissures, but may also occur in parts distant from these. This would explain salivary gland tumors occurring in the orbit, soft palate, and gums. He states that the occurrence in, or around, a salivary gland is purely coincidental.

Hellwig believed that these mixed tumors originated from the notochord and felt that this best explained the presence of the wide variety of tissues found.

A good review of histogenesis has been outlined by Kraissl and Stout, Freshman and Kurland, and by Oden.

Theories presented below are to explain papillary cystadenoma lymphomatosum.

(a) A blending of the preauricular lymphatic material with the parotid lobule, and this portion making up a lobule separate from the parotid gland. This would explain the appearance of papillary cystadenoma lymphomatosis.

(b) Warthin postulated a heterotopia or dystopia of pharyngeal entoderm in or about the

parotid gland. He feels that the cells, particularly those lining the cysts in papillary cystadenoma lymphomatosum, resemble the lining of the eustachian tube. He felt that cilia were occasionally present on these cells, but this has not been corroborated by others.

(c) Harris speaks of heterotopic salivary gland epithelium in lymphoid tissue.

(d) Failure of extrusion of lymphoid tissue in the developing salivary gland.

(e) Misplaced thymic anlage.

(f) Ectopic tonsillar inclusion.

(g) Metaplasia of the epithelial lining of lymph spaces.

(h) Lymphoid embryonic rests.

(i) Orbital node inclusion. This is an embryonic structure, the fate of which is unknown in man.

(j) Hamferl describes peculiar epithelial cells which he calls oncocytes. These cells are possibly derived from duct lining, which metaplasia are capable of developing into many different types of tissue.

(k) Mazza, Cassinelli, Glass seem to agree that these tumors have a branchial origin.

(l) Jaffe describes "secretion capillaries" and explains the cystic spaces on increased secretion. He recalls that the parotid gland often contains lymphoid tissue and believes this, plus aberrant gland tissue, explains these tumors.

(m) Riskl, Montier and Redon believe that the origin is from duct epithelium. Murray has shown that neoplastic cells growing in situ may evince some of the characteristics of the normal tissue from which they arise. Comparison with normal tissue growths from fetal parotid gland reveal that growths are in a similar pattern and seem to indicate an origin from duct epithelium.

Considering all the above data, one must conclude that there is no proven origin to parotid tumors. The consensus of opinion, however, seems to point to an epithelial origin, most likely due to displaced cells of the tubular structure from which the adult gland develops.

Relative to the origin of muco-epidermoid tumors, Stewart *et al.* feel that they developed from mucous cells which are normally present in small numbers in the duct wall. It has been seen that these multiply greatly under certain conditions, especially in chronic inflammation of the gland, then by metaplasia and hyperplasia the various cell components seen in these tumors are produced.

A simple explanation of tumors of the salivary glands is to assume that they arise from adult gland tissue and the weird and bazarre structures seen are merely those which have occurred due to metaplasia and metamorphosis. It is true that in some cases a direct and gradual change from the normal gland to that of the tumor can be seen. In some mixed tumors, there is an attempt made by the epithelium to form alveoli. There is no "typical" mixed tumor as there are so many variations in structure.

III

NEOPLASMS OF THE SALIVARY GLANDS

BENIGN TUMORS

I. Adenoma. True adenomas are exceedingly rare but a few have been seen and reported. Wheelock and Madden describe and illustrate one such case. Slaughter *et al.* report one case. We have had one in our series (see Fig. 1).

II. Mixed Tumors *(Pleomorphic Adenomas).* The multiplicity of names for these tumors is confusing. There is also a wide range of theories of histogenesis. Willis clarifies the situation when he concludes that these tumors are not "mixed" but arise from and consist of salivary gland epithelium only. They contain no mucous connective tissue and no true cartilage except in rare instances. In these cases, the presence of cartilage can be explained on the basis of metaplasia in the connective tissue. The pseudocartilage may be readily explained as an alteration of the mucinous pools which characterize these tumors. Willis prefers the name "pleomorphic adenomas."

A. Age Incidence. Tumors may occur at any age but most frequently between 20 and 40 years. They are uncommon in children. Schilling reported a tumor removed at the age of 41 which began at the age of one year.

B. Sex Incidence. Usually more females are affected as seen in various studies. In McFarland's 396 cases, 212 were females. However, in Chevassu's 57 cases, 27 were females and 30 were males.

C. Site. 428 cases from Patey, Zymbal, Harvey *et al.*, Wallace were as follows:

Parotid	83 per cent
Submaxillary	8 per cent
Sublingual	1 per cent
Palate	4 per cent
Lips and other sites	4 per cent

D. Structure. The structure of the mixed tumor is exceedingly variable. In some tumors many or all of the variations may be seen and all graduations between them. In other tumors, one type of cellular pattern may predominate. Some of these patterns may be described as follows.

1. Where nearly normal-appearing salivary tissue exists.

   In these, acinar and tube-like structures are seen deep in the mucinous stroma. Willis feels that these are portions of salivary tissue which have participated in the neoplastic change along with these attached lobules of acini. In this instance, the acini and ducts clearly resemble that of normal gland.
2. Less typical glandular tissue is often seen and may form sheets of tissue assuming convoluted and anastomosing pattern.
3. Sprouting or spraying of the epithelial strands into the surrounding mucinous material.
4. Epithelial masses in solid cords may often be seen.
5. Epithelial masses may have cystic spaces and may even be described as cribiform or honeycomb in pattern.
6. Some epithelium may develop epidermoid characters and even show stratification and cornification.
7. A network of epithelial cells in a matrix of the mucinous material is quite common.
8. Some show a more cellular and anaplastic picture with mitotic figures, indicating malignant change.

E. Stroma and Capsule. The mucinous and pseudocartilagenous areas belong to and are derived from the epithelial parenchyma of the tumors. Changes in the stroma of these tumors include fibrosis, alteration of elastic tissue, hyaline changes, collection of leucocytes, calcification and in rare instances osseous or cartilagenous metaplasia. Again, it is emphasized that those changes come from the stroma and not the parenchyma.

Willis says that increase of collagen may occur

around epithelial tubules or solid strands giving rather characteristic pictures often referred to as cylindromatous. He thinks this gives the erroneous idea that the tumors are endothelial in origin.

It may be seen, therefore, that any one description of these tumors would be difficult and inadequate. Leroux, Lerous-Robert and Delanglade presented 10 different variations.

F. Relationship of Tumor to Surrounding Normal Salivary Gland Tissue. Willis has noted and illustrated by photomicrographs how the gland and tumor may fade into each other by direct transition. These areas show a gradual alteration of the normal gland epithelium to tumor tissue with its mucinous or pseudocartilage area. He believes that these clearly show the direct origin of the tumors from salivary gland tissue.

G. Encapsulation of Mixed Tumors. "Encapsulation" is a common but erroneous term. The capsule may vary greatly in width and density. In one case (see Fig. 3) there was an area where no capsule existed. Nothing separated the tumor and normal gland tissue. In Figure 4 and Figure 5, there is a capsule but this is infiltrated by tumor cells. One might say there is a gradual transition right through the capsule from normal gland to tumor. At operation, the tumor may appear sharply delineated grossly but a study of the microscopic section may reveal penetration of the capsule. Therefore, it is obvious that "enucleation" is inadequate.

H. Rate of Growth. The rate of growth of the original tumor is characteristically slow. The duration before surgery has varied greatly from six months to as much as 44 years (one case from Bland-Sutton and another case of Wilson and Willis' series). The author had one case, the duration before surgery being 60 years (see Fig. 6). The average duration before surgery is about seven years. It must be emphasized that a long duration does not lead to the conclusion that the tumor is benign. Malignancy may be present for several years or there may be a recent malignant change.

I. Recurrence. Recurrences may also be slow. Patey reported one recurrence after 19 years and McFarland one at 47 years postoperatively. It is difficult, therefore, to estimate the prognosis. The longer case series are followed, the higher will the rate of recurrence be. Willis felt that of those patients alive after five years, 48 per cent would have recurrences; but if the series were followed seven years, the recurrence rate would be 62 per cent.

The liability to recurrence is due to several factors. Probably the most important factor is inadequate and poorly conducted surgical procedure. We have noted above that the capsule cannot be relied upon to encompass all the tumor. Therefore, "enucleation" should be discarded as inadequate. Multicentric tumor foci are sometimes seen. This is very frequently seen in recurrences. Clearly, then, local removal of a tumor is inadequate surgery.

J. Degree of Malignancy. The mixed tumors (pleomorphic) are usually spoken of as benign because of their slow growth, their supposed encapsulation and the rarity of metastases. Those who have had the most experience with these tumors now regard them as malignant. It is difficult to estimate the behavior of a tumor by the histological pattern. There is no doubt that many tumors, apparently benign and slow growing, do take on rapid growth and obviously there has been a change. Whether there has been malignancy from the start is questionable. There is plenty of evidence to show the transition from a mixed tumor to one of serious malignancy. Dockerty classifies these "mixed" as adenocarcinoma (mixed tumor type). Certainly at least 25 per cent of tumors which are removed are very definitely malignant.

When mixed tumors recur, the histological picture is usually altered and they exhibit borderline or frank malignancy (see Cases 9 and 10 with photomicrograph). This is shown in most cases by increased cellularity. Other characteristics of malignancy may be present such as increased mitosis and invasive tendency. Some recurrent tumors do not exhibit any of the above changes. This is illustrated in Figures 7, 8, and 9. These represent the original tumor and two recurrences. Some primary tumors show increased cellularity to such a degree that a borderline

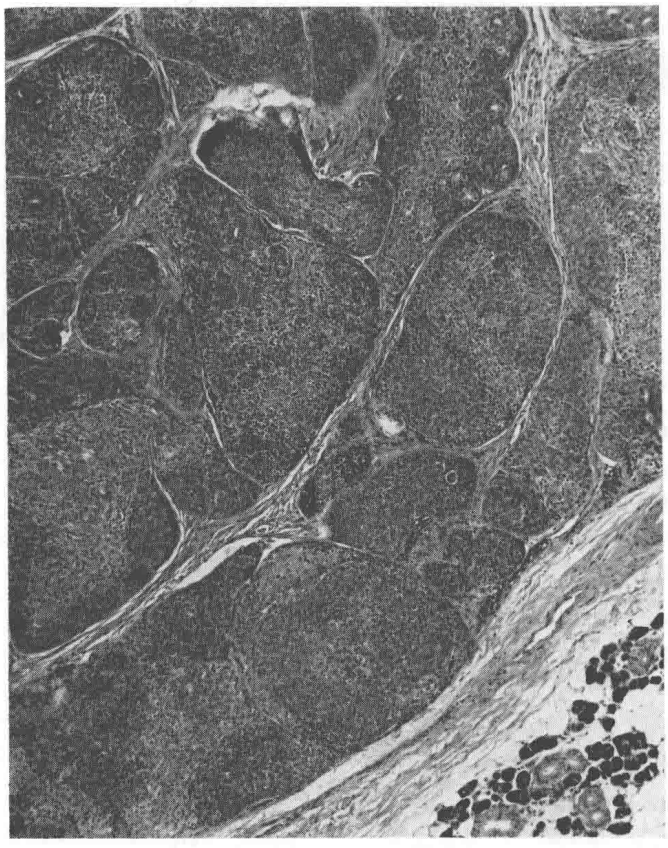

FIG. 1

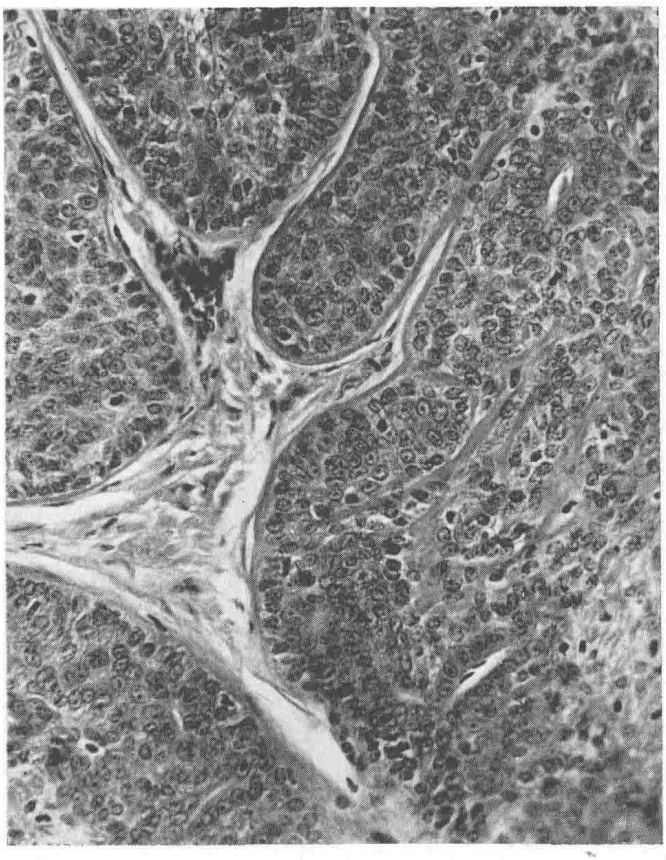

FIG. 2

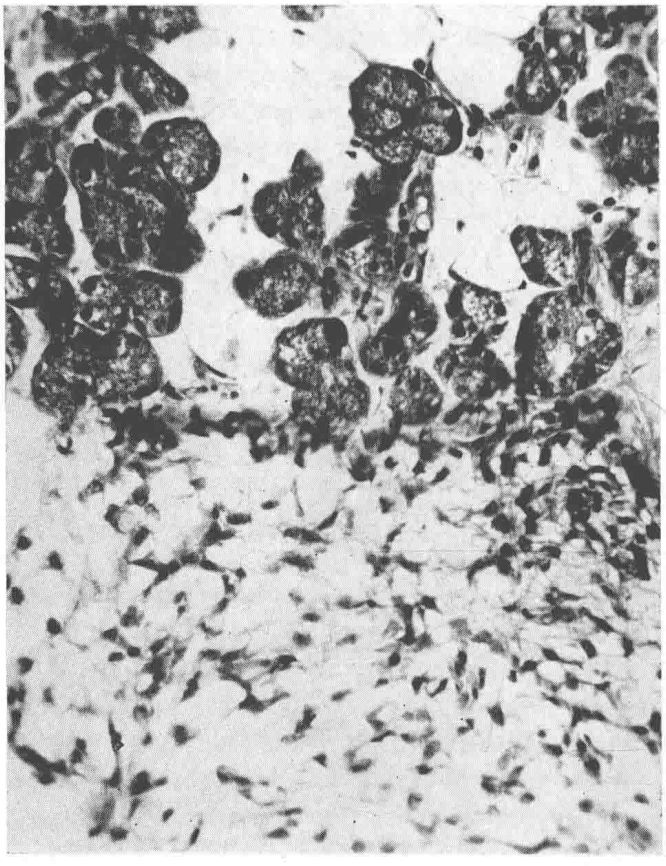

FIG. 3

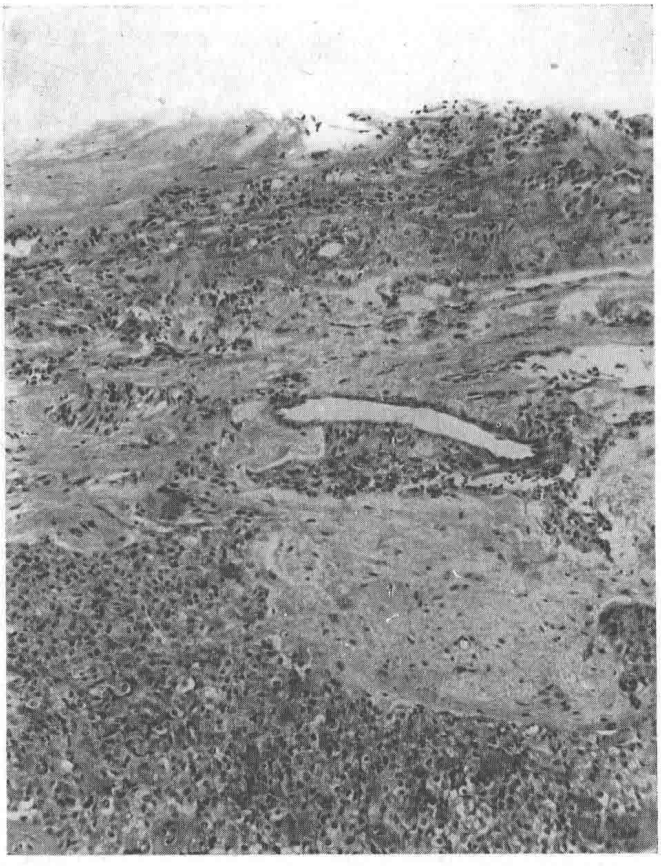

FIG. 4

malignancy must be suspected (see Figs. 11, 12, 13 and 14).

III. Muco-epidermoid Tumors *(See Figs. 15 to 17c).* Whether these represent still another variance in the so-called mixed tumor is debatable. Nevertheless, their behavior pathologically and clinically gives them a deserving separate classification as a definite group. Stewart, Foote and Becker have described these tumors and give them the name "muco-epidermoid tumors." For more detail the reader is referred to their excellent paper. The following data has been extracted from their article.

The frequency is about 5 per cent of tumors of the salivary glands. As a group, they traverse an unusually wide variation in histologic appearance since there is a tendency to diffuse overgrowth by a single cell type. The characteristic element, which can be demonstrated in most cases is the presence of mucous cells, as shown by staining with Mayer's mucicarmine.

The origin of these tumors is presumed to be from the sparce mucous cells seen in the normal ducts. Under certain circumstances, these can proliferate and take part in the formation of a tumor. Other cells in the duct include rounded basal or malpighian cells, intermediate cell types and the columnar cells. Any one of these cell types may predominate in various tumors. Structural patterns are therefore numerous and varied.

Besides the mucous cells in these tumors, the other characteristics seen is epidermoid metaplasia. These cells are thought to originate from the basal cell layer and by metaplasia may form larger cells, some polygonal in outline and a later development may be epidermoid cells three or four times the original basal cells and may be described as possessing squamous character. These cells possess great power of proliferation. The most characteristic tumors are those which contain reasonably large numbers of all the various cell types.

Where basal or intermediate cells predominate, a uniform mosaic pattern results, tending to form wide sheet-like masses. The mucous cells may form duct-like structures or even cystic spaces partly filled with mucoid secretion. Such mucous pools may rupture through into adjacent tissue where a marked secondary reaction may occur. Where epidermoid cells are in excess, they may resemble malignancy. However, there is a monotonous regularity of structure which differentiates it from carcinoma. In a few cases, there are certain areas where the cells

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FIG. 1. Adenoma of Salivary Gland. This patient had a mass of three years' duration which was removed in 1938 and has gradually recurred. The above photomicrograph represents a section removed on 11-23-45. Total parotidectomy was done. Within the mass of tissue removed, there was a discreet nodule 1.5 cm. in diameter. The cut surface was grayish-white and seemed to be divided into lobules. Microscopic examination shows a circumscribed, well-encapsulated tumor. The tumor cells are composed of well differentiated epithelial cells occurring in irregular groups separated by strands of fibrous connective tissue. Most of the cells are transitional in type. Others are columnar and these are arranged in somewhat distorted glandular formation. The nuclei are uniform in size and show no pleomorphism. There has been no recurrence since. (E-2847-45)

FIG. 2. Adenoma. This represents a high power photomicrograph (#2 high power) on the previous slide of benign adenoma of the salivary gland. It again shows masses of tumor cells most of which are of the transitional type. Strands of fibrous tissue tend to separate these masses of tumor cells into a lobular structure. (E-2847-45)

FIG. 3. Mixed Tumor of the Parotid Gland. This tumor was situated in the left parotid gland and the tumor mass was approximately 11 mm. in diameter. The microscopic picture of the tumor tissue is not remarkable. The tumor cells are composed of multiple, small, uniformly sized epithelial cells unevenly distributed against a mucoid background. The cells have ovoid, spindle-shaped and stellate nuclei. Many of the cells occur in linear strands and in slender anastomosing cords. There is partial encapsulation. The photomicrograph is submitted to show normal glandular tissue in the upper half of the picture, embedded in a fatty background. The tumor is seen in the left half of the picture and it will be noted that at this particular point there is absolutely no capsule. "It is obvious that enucleation would not be adequate in this case." (E-4553-51)

FIG. 4. Mixed Tumor of Salivary Gland. The above photomicrograph is that of mixed salivary gland tumor presented to show that the fibrous tissue capsule is infiltrated by the tumor. Here again we hope to emphasize that only by wide radical surgery can such a tumor be adequately removed. (E-4537-47)

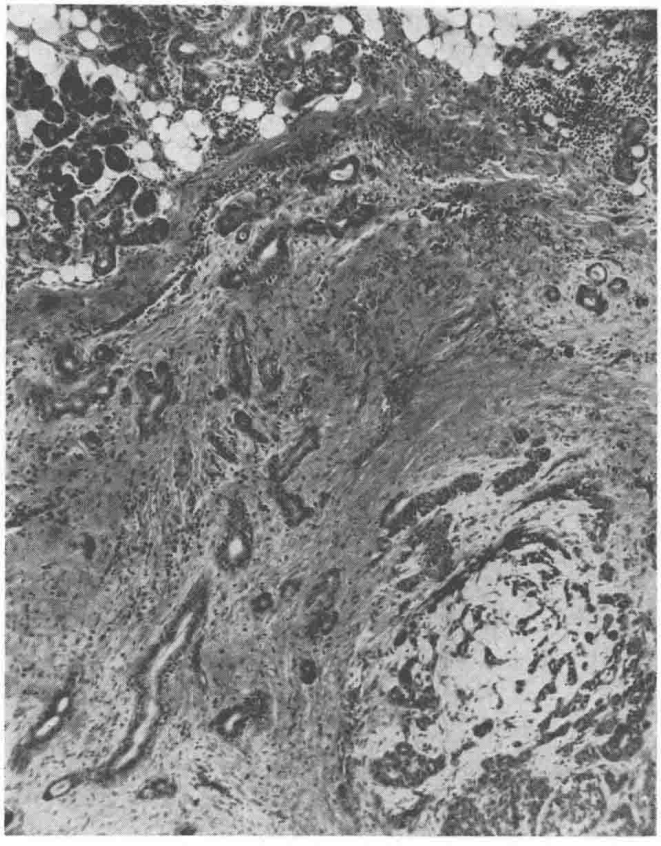

FIG. 5

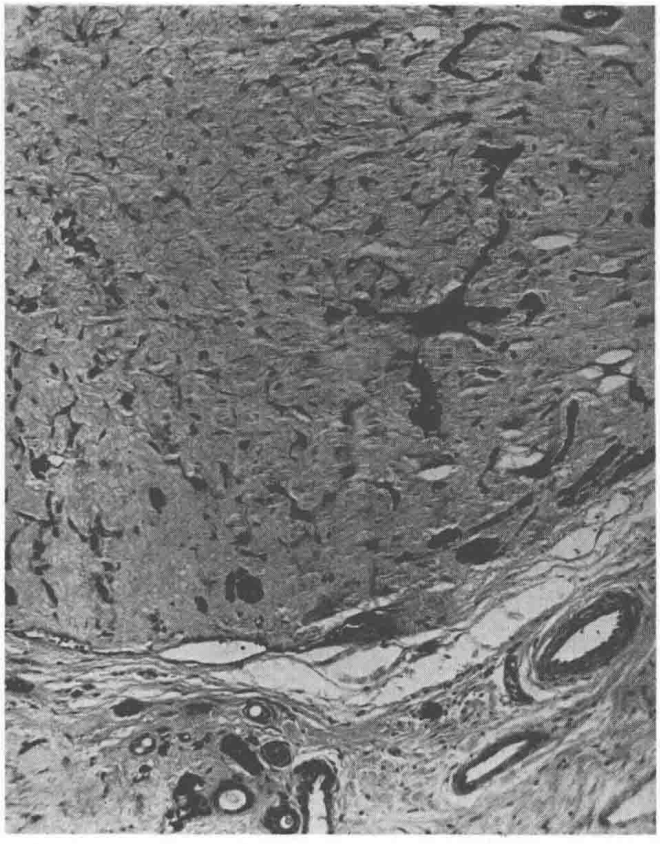

FIG. 6

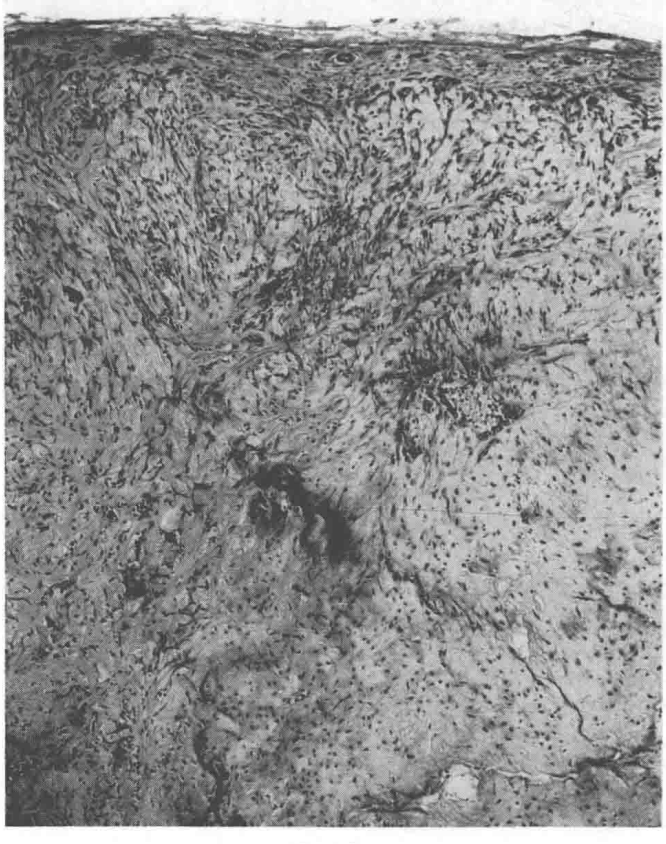

FIG. 7

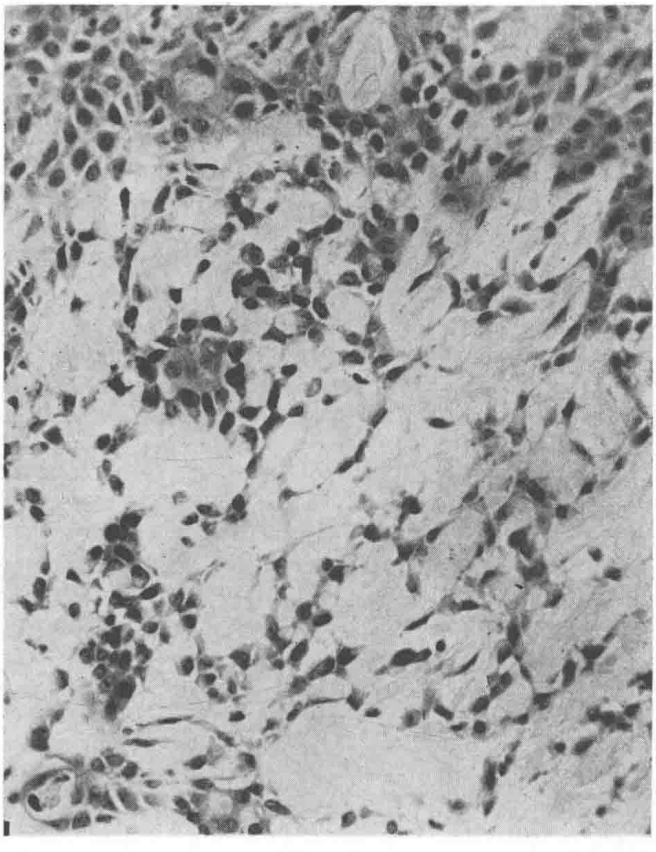

FIG. 8

are swollen and clear, resembling clear cell renal adenocarcinoma.

When malignancy is present, we see little tendency to microcytes. Tubular and papillary features are less common. The formation of mucus is at a minimum. Epidermoid cells predominate but staining with mucicarmine will show positive mucous reaction. Usually, it is easy to distinguish a malignant tumor from the benign. The borderline cases may be difficult but the chief distinguishing feature is their outstanding characteristic to diffuse proliferation of rather small, moderately hyperchromatic, rounded and oval cells in sheet-like arrangement with tendency to palisading of the outer layer of cells which surround the proliferating sheets and pegs of tumor. Oversecretion of mucus with the formation of mucous pools practically never occurs.

A. Gross Pathology of Benign Tumors. The tumor is usually small (less than 4 cm. in diameter). They are oval and fairly well circumscribed but poor encapsulation or even absence of encapsulation is the rule. (In only four out of 26 cases was there a well developed capsule, Stewart *et al.*) The tumors are firm but not hard. Cut surfaces are grayish-white or grayish-pink. They are mostly cystic, usually showing multiple small cysts containing mucoid material.

B. Gross Pathology of Malignant Tumors.

FIG. 5. Mixed Tumor of Salivary Gland, Recurrent. Clinically, this patient had had a previous biopsy; the tumor seemed to be infiltrating in nature. We felt at biopsy there was not a clear-cut, definite border. At this operation the whole superficial lobe was removed. In this specimen we found the residue of tumor tissue, part of which had been removed by the former biopsy. Photomicrograph of section of the parotid tumor shows a circumscribed nodule. It appears to be made up of tumor cells distributed in strands and separated by abundant mucinous stroma. Some of the cells are arranged in disordered glandular patterns. The capsule consists of dense fibrous tissue. However, as can be seen in the above photomicrograph, there is a gradual gradation from normal salivary gland situated in the upper left corner to tumor tissue which infiltrates through the capsule and blends with the tumor tissue. This indicates again that enucleation is inadequate in removing these tumors. (E-307-45)

Note: In spite of the wide removal this tumor recurred four years later. The recurrence consisted of several nodules beneath the skin. It is our opinion that probably some tumor cells were spread by the previous biopsy. We feel that biopsies are dangerous as they cut into the tumor tissue and spread the tumor cells.

FIG. 6. Mixed Tumor of Parotid Gland. The patient from which the above photomicrograph was taken had the tumor for over 60 years. She presented herself for surgery because of increased rapidity of growth. A malignancy was suspected and a total removal of the parotid gland was performed. A section of the tumor which measured 3.5 × 2 × 2.5 cm. shows an encapsulated tumor. There is a background of mucinous stroma which in places has an appearance of poorly developed cartilage. Scattered throughout this background are irregular groups of epithelial cells. Some are arranged in glandular patterns. Others occur in small solid groups and others are in linear strands or anastomosing cords. The nuclei are small. Some of them are hyperchromatic. There is no appreciable degree of pleomorphism. (E-341-50)

FIG. 7. Mixed Tumor of the Parotid Gland, Recurrent. This is a recurrence of a tumor operated in 1939. The slide and tissue are not available but the report reads as follows. Histological examination shows solid, cellular strands composed of deep blue staining cells of epithelial type. In places the stroma shows hyalinization. In places the tumor is enclosed within an intact hyaline connective tissue capsule. In other areas the capsule is thin and compressed. In one area the tumor extends through the capsule. The operation was enucleation. Therefore it is not surprising that there was a recurrence. (533-39 E) Photomicrograph No. 7 shows the recurrent tumor. A complete parotidectomy was performed in 1942. The tumor did not exhibit any increase in cellularity which in our experience is unusual. The histological picture is epithelial elements in a mucinous background in which areas of pseudocartilage exist. The epithelial elements occur in irregular strands and fine cords. Most of the nuclei are spindle shaped. (E-1660-42)

FIG. 8. Recurrent Mixed Tumor of the Parotid Gland. This is the third operation, the last one was in 1944. There has been no recurrence after 10 years. Specimen consists of a mass of reddish-gray tissue measuring 7.5 × 4 × 3.5 cms. There are at least three separate and distinct encapsulated tumors. The tumors are cartilagenous in consistency and pale gray in color. The tumors are composed of strands and anastomosing cords of epithelial tumor cells separated by a very mucinous stroma. Some of the cells are arranged in glandular pattern. The nuclei are uniform in size and show no appreciable degree of pleomorphism. The behavior of this recurrent tumor is typical in that nearly always there are multiple tumors. Photomicrograph No. 7 shows the first recurrence and the text describes the original tumor.

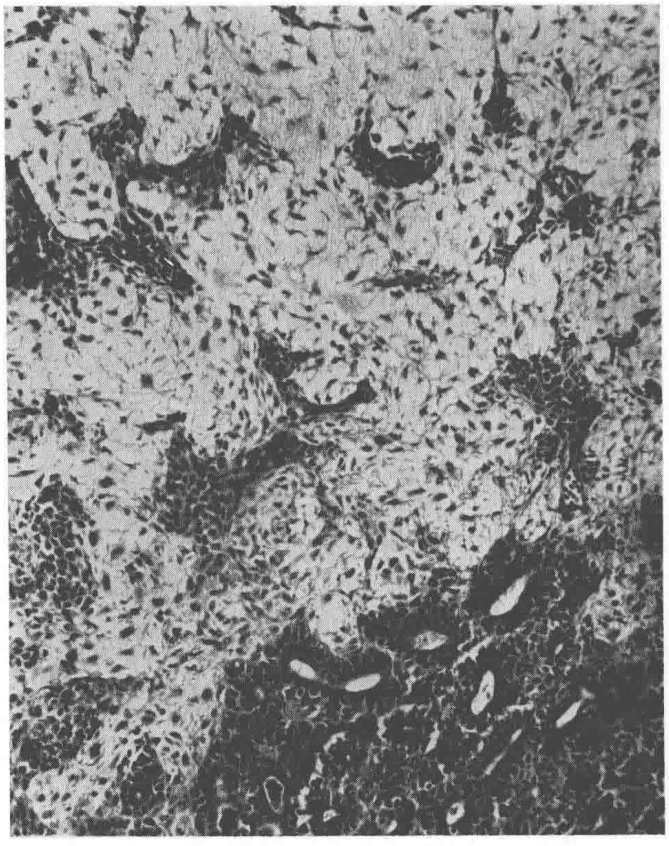

FIG. 9

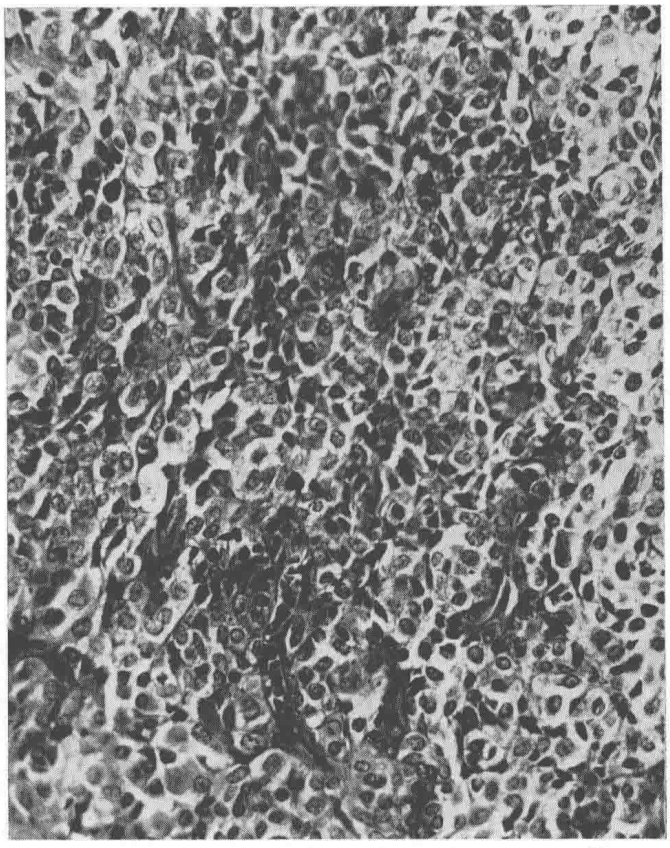

FIG. 10

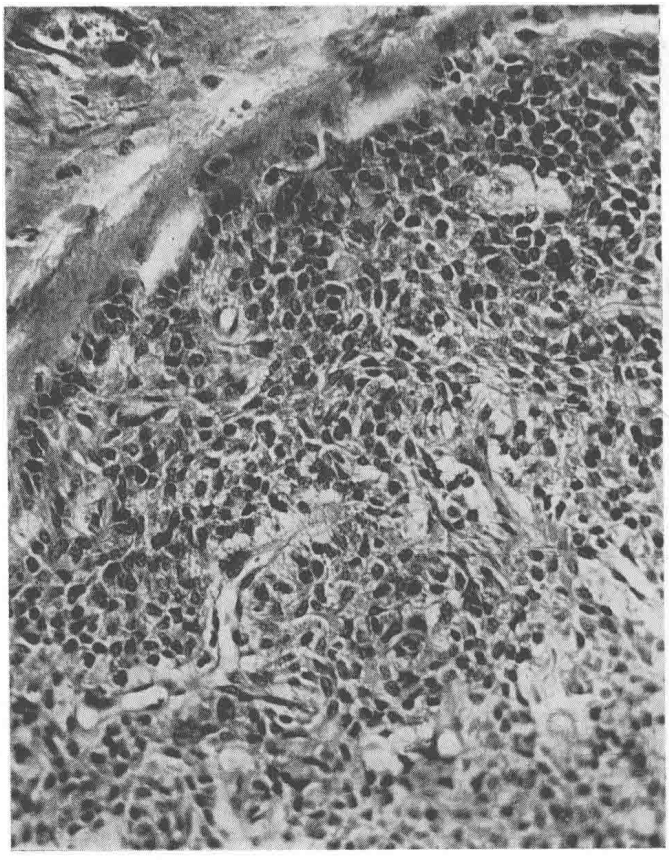

FIG. 11

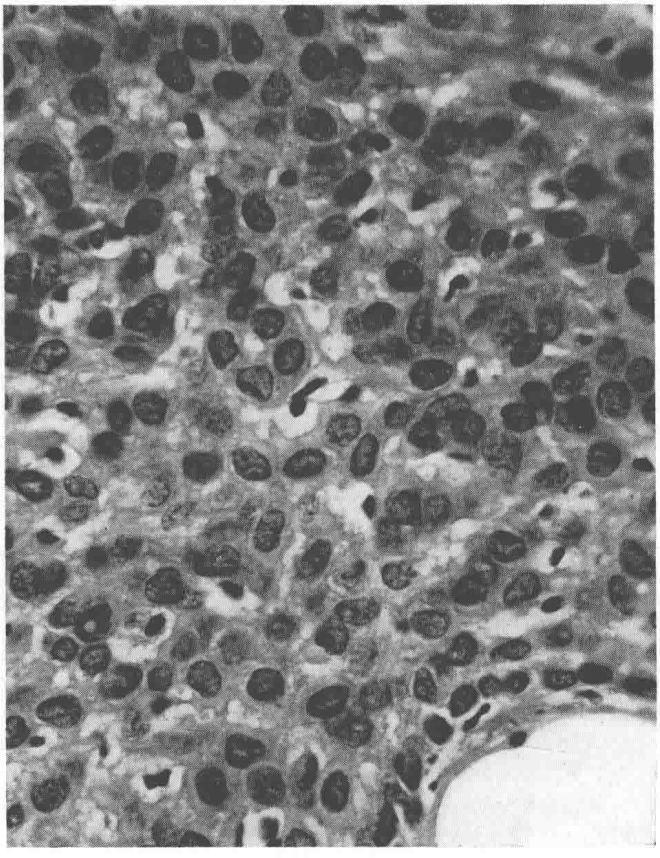

FIG. 12