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Mixed tumors of salivary gland type

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MIXED TUMORS
OF
SALIVARY GLAND TYPE

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INTRODUCTION

It is the purpose of this paper to review some of the great amount of literature on the so-called "mixed tumors" with reference to their location, occurrence, composition, treatment, prognosis and origin.

DEFINITION

The term "mixed tumor" is used in two distinct ways. In its simplest implication, the term is applied to lesions in which two adult tissues are active in the neoplastic process, such as the myofibromo or lympho-epithelioma. The more exact use of the term is restricted to two tumors--the so-called "mixed tumors" of the salivary glands and of the kidney. In these tumors it has been generally conceded through the years that there are at least two germ layers represented, which have arisen from partially differentiated somatic blastomeres. Today, the "mixed" tumors of the kidney are more often regarded as teratoid tumors with their own distinct origin. Thus, through elimination, the term "mixed tumor" as discussed in this paper, will be confined to neoplasms of salivary glands and oro-facial region or tumors resembling those found in this region.

Mixed tumors contain more than one type of tissue in the neoplastic process just as the teratoma or dermoid cyst does. The teratoma and dermoid, however, attempt to form distinct tissue--the character of which can be identified. The mixed tumor does not form definite structures, but has the epithelial and meso-thelial elements mixed and in intimate contact with no division between the two types of tissue. Some workers,

however, still regard the mixed tumor as a type of teratoma. Fox, 1939, states, "Mixed tumors in or adjacent to the salivary glands come under the classification of teratoms. They contain tissue cells originating in the ectodermal and mesodermal embryonic layers." Levin, 1940, says, "The mixed tumor develops as a malignant transformation of a teratoma . . . not within the fully developed teratoma but as a transformation of a germinal rest."

Eggers, 1928, states, "The term 'mixed tumor' applied to neoplasms of complex structure is unsatisfactory since it gives no idea of derivation, but is probably most applicable since it gives an idea of composition but leaves the origin obscure."

Sheldon, 1943, considers mixed tumors of the salivary glands as cancerous or non-cancerous neoplasms composed of one or two different types of neoplastic cells, and he also states that neoplasms of similar appearance have been found in the skin, lacrimal glands and breast. Virchow, who first described the tumor in 1863, called them enchondromas and thought they were of mesoblastic origin, but since epithelial elements were also present, he called them "mixed" tumors.

Ewing says that the term "mixed tumor" is now used to designate those relatively simple, embryonal tumors which are entirely of local origin--the result of

proliferation of embryonal structures. Bland-Sutton, 1922, voiced the opinion of many workers in this field when he stated, "Tumors of the salivary glands are a pathological puzzle and a source of much unsatisfactory speculation."

Harvey, Dawson, and Innes, 1938, define mixed tumors as adenomas of the serous and seromucous salivary or lacrimal glands, of undifferentiated and gland-lobular types, which are very prone to a species of mucoid autolytic self-destruction transformation of their component tissues and are seldom truly malignant.

Patey, 1935, concluded that the mixed tumors of the salivary glands are a composite group of epithelial tumors, the varying pathological features of which depend on the degree of differentiation attained, the rapidity of division of the cells, and the amount of myxomatous change undergone by the epithelium. According to the degree of change, all gradations may be encountered between a myxoma on one hand and a highly differentiated tumor with ducts and acini on the other, and between a slowly growing tumor with regular cells or an irregular anaplastic growth.

Judging by the different definitions quoted, it is plain to see that there is considerable controversy over what constitutes a mixed tumor and what its origin is.

OCCURRENCE

LOCATION

Mixed tumors are usually found in the salivary glands and oro-facial region including lacrimal gland, tongue, palate, pharynx, and lip. Sheldon, 1943, states that similar tumors have been found in the skin and breast, while Harris and Schattenberg, 1942, describe four tumors in the lungs which resemble the salivary mixed tumors. The parotid gland and surrounding tissue is by far the most frequent site of the mixed tumor. McFarland, 1942, presented a collection of 421 cases of mixed tumors of which 380 were in the parotid region, 12 in the submaxillary region, and 2 in the sublingual region--the remaining cases were incomplete as to history or proof of identity. McFarland states that the angioma, Hürthle cell tumor (onchocytoma), neurofibroma, or branchiogenic carcinoma may be mistaken for a mixed tumor. He later presented a revised series of 413 cases (1943) with 389 in the parotid, 12 in the submaxillary and 2 in the sublingual region. Mulligan, 1943, reported a series of 20 cases of malignant mixed tumors of the salivary glands of which 12 were tumors of the parotid, 8 in the submaxillary, 2 in the hard palate, and 1 in the sublingual gland.

Smith, 1939, gave a summary of reported cases of

mixed tumor of the sublingual gland. He states that over a period of forty years at the Pathology Department of St. Luke's Hospital 135 mixed tumors have been reported with only one in the sublingual gland. He quotes figures compilled by other workers which emphasize the rarity of sublingual mixed tumors. They are as follows:

	Sublingual	Parotid
Greenberg	1	30
Patey	1	45
Chur and Loucks	0	37
Martin and Elkin	0	24
Ahlbom	2	202
McFarland	1	297
Shore (St. Lukes)	1	135
	6	770

Brunschwig, 1939, reviewed the literature and reported only three cases of mixed tumor of the sublingual gland and ten cases of tumor in the tongue. Dockerty and Mayo, 1943, reviewed 500 cases of submaxillary tumors but accepted only 81 as true mixed tumors. They state that submaxillary tumors occur once in every twenty thousand admissions to the Mayo Clinic and are only one tenth as common as parotid tumors.

Woodson, 1942, reported a case of mixed tumor of the pharyngomaxillary space and states that the Quarterly Cumulative Index Medicus has carried reports of only two such cases since 1930.

New and Childrey, 1931, reported 357 cases of tumor of tonsils and oropharynx. Of these, 76 were adenomas of mixed tumor type and 56 per cent were in the palate while 44 per cent were in other tissues of the

oropharynx. Gaylor and Smith, 1931, state that mixed tumors of the larynx or esophagus are rare although they do occur. New, 1920, feels that such tumors are not directly related to mixed tumors of the face, mouth or oropharynx. He reports a case involving the vocal cords in which the patient recovered following complete excision of the vocal cords

Wood, 1904, reviewed a series of 59 "salivary" tumors with four in the lip, four in the pharynx, two in the neck, and one in the cheek. He gives the frequency of submaxillary to parotid tumors as 1 to 10, and considers sublingual tumors about one per cent. His own cases consisted of 26 in the parotid and 13 in the submaxillary gland.

Eggers, 1928, compiled from the literature over one hundred mixed tumors of the palate, 92 of which he considered to be sufficiently verified. He states that though tumors of the palate are rare, they are still the most common outside of the parotid and submaxillary glands. Eggers calls attention to the fact that mixed tumors occur almost exclusively in the adult while teratomas are found mostly in the young. He reports five cases of palate tumors. D'Aunoy, 1930, reported two cases of mixed tumor of the palate.

Wilson and Willis, 1912, reported a series of 56 cases of mixed tumor treated surgically at the Mayo Clinic from January 1, 1905 to April 10, 1911. Fifty were in the parotid and six in the submaxillary gland.

Verhoeff. 1904, reported five cases of tumor of the lacrymal gland. He states that owing to their situation the tumors of the lacrymal gland are not only dangerous to sight, but are more dangerous to life than those of the salivary gland and should be extirpated as soon as possible. Neely, 1937, states, after a review of the literature, that up to the present, 267 cases of lacrimal gland mixed tumor have been reported. The first case was reported in 1598 by Fabicius Hildanus.

Fry, 1927, reported on 25 mixed tumors removed at St. Mary's Hospital, London, between 1912-23. Of these tumors, 17 were in the parotid region, 5 in the submaxillary region and three were unknown as to location. Patey, 1931, reported a series of 55 cases of salivary gland tumor treated in the Middlesex Hospital since 1919. In this series, the location of the tumor was 38 in the parotid, 6 in the submaxillary, 5 in the palate, one in the sublingual, one in the lip, one at the angle of the mouth, one on the face, one in the tongue, and one of unknown location.

Simard, 1938, reported a case of mixed tumor in a woman 76 years old. The tumor was on the hypothenar region of the left hand and was about the size of a pigeon's egg, hard and resistant to pressure and attached to deeper tissue. It started as a small

subcutaneous nodule which grew progressively and was 5 x 4.5 x 4.2 cm. in size at removal.

Kreibig, 1931, reported two cases of mixed tumor in unusual locations. One, the size of a hen's egg, was on the anterior tibia of a 38 year old man and was attributed to trauma six years previous. The other, in a 30 year old man, had appeared three years before on the proximal forearm and was the size of a hazelnut.

Tessman, , described a tumor called a chondro-endothelio-myxoma which had been present for four years on the back of the hand of a middle-aged woman.

Hirsch, 1933, reported a mixed tumor as large as an apple in a 38 year old negress which arose in connective tissue of the thigh above the patella. Vidari, 1935, saw a mixed tumor on the calf of the leg of a 48 year old man which had been present since childhood. It had undergone rapid growth only a short time previous. The tumor was readily enucleated.

Gaehtgens, 1934, described a mixed tumor about the size of a cherry which was encapsulated and multilobular and had been present for about two years. It was located on the fourth finger of the right hand of a 60 year old woman. Scharla, 1936, supplied a case of a 30 year old woman who had a tumor on the fifth finger of the right hand. This tumor was the size of a hazelnut, hard, lobulated, well-defined and movable, and had not recurred a year after removal.

Eggers, 1938, reported a case of mixed tumor of the upper lip in a man 60 years old who had first noticed a lump following a pitchfork wound 35 years previous. The lump grew slowly until two years before when it began to increase rapidly in size and at removal measured 1.3 x 1 x 1 cm. Eggers compilled a series of 64 cases from the literature and states that mixed tumors are more frequent in the upper than lower lip. This fact may be explained by the more complicated development of the upper lip.

Pilcher, 1937, reported a case of a man 49 years old who had a slow-growing, painless swelling on the upper lip for twelve years, which was diagnosed as a mixed tumor. The tumor first appeared after a blow on the lip from the starting handle of a motor.

AGE AND SEX INCIDENCE

The age of patients treated for mixed tumors shows a wide variation. Eggers, 1928, however, states that mixed tumors are found almost exclusively in the adult. D'Aunoy, 1930, states that tumors of the palate can occur at any age but are more common in the second, third and fourth decades, and they show no sex predilection.

Wilson and Willis, 1912, analyzed 56 cases of mixed tumors and concluded that two-thirds of the cases appear under 40 years, one-half occur between 20 and 40 years, and the sex ratio is nearly equal with a slight preponderance in males. Fraser, 1918, states that mixed tumors arise from the ducts of adult glands. Wood, 1904, reported, in his series of 59 cases, most occurred during the second decade.

Dockerty and Mayo, 1943, reviewing 81 cases of submaxillary tumor, give the average age of incidence at 39 years, and fifty per cent were between 20 and 40 years. The average age for the cylindroma type of malignant mixed tumor was ten years later--eleven cases being between 40 and 50 years. Mulligan, 1943, cites a series of 20 cases of mixed tumors with metastases in which the patients, when first seen, were between the ages of 31 and 65 years, and the sex ratio was 8 males to 13 females.

Harvey, Dawson, and Innes, 1938, state that in their series of 316 cases, ages at operation ranged from 15 to 89 years.

McFarland, 1942, gives sex incidence of mixed tumors in his series as 184 in males and 212 in females.

MICROSCOPIC STRUCTURE

Mixed tumors show a large variety of apparently different types of tissue. Simple columnar, simple cuboidal, stratified cuboidal, stratified squamous, and simple squamous epithelium, fibrous connective tissue, mucoid connective tissue, cartilage, and bone have all been identified by various workers who have studied the micro-anatomy of these tumors.

Harvey, Dawson, and Innes, 1938, give the following description of mixed tumors.

"The epithelial component which is the characteristic element of the tumour is essentially of glandular type. The cells are mainly undifferentiated in character, but may develop some degree of differentiation along either glandular or epidermoid lines, or both. The glandiform elements, when present in the tumour, may consist of acini with one layer of cubical or columnar epithelium, or of ducts with two layers of epithelium, or of spaces lined with numerous layers of uniform cells. Some of the cell-complexes may be of basal-cell type and may be cystic, with mucoid, colloid or hyaline content or no content at all. In another direction and probably affording an instance of metaplasia of undifferentiated cell elements, the tumour cells exhibit epidermoid character, not only as basal cells but more strikingly as squamous cells with intercellular bridges, keratohyalin granulation and 'pearl' formations. In the main, however, these tumours consist rather of undifferentiated polyhedral or spindle-shaped cells arranged in parenchymatous masses, irregular anastomosing strands of closely packed uniform basophilic cells, without indication of keratinization. The nucleus is hyperchromatic and a nucleolus may or may not be evident. The scanty cytoplasm is faintly acidophile. Mitoses are scarce, except when the tumor is truly malignant. The very varied cellular picture presented by this tumour led, in the past, to certain features being picked out which determined its nomenclature as myxomatous, endotheliomatous, cylindromatous, chondromatous, basiliomatous, carcinomatous, sarcomatous and combinations of these. The endothelial or sarcomatous designations have lapsed with the more or less

general acceptance of the epithelial elements as the essential component of the tumour. The tendency of the epithelium, and of the stroma also, to show myxoid, hyaline and chondroid transformations or 'inclusion' area have been taken to be true cartilage. Such cartilage has, however, little resemblence to fetal cartilage and is without perichondrium."

Eggers, 1928, is his compilation of palate tumors, arranged them is seven groups according to microscopic appearance. They were as follows.

1. Those which showed a predominence of columnar epithelium with pearl formation and tubules with several layers of cuboidal cells. The stroma is infiltrated with squamous epithelial cells. The stroma is mucoid connective tissue with areas of hyaline connective tissue suggesting cartilage matrix and occasional groups of fat cells. A connective tissue capsule surrounds the tumor.

2. Those consisting mostly of cartilage matrix with cells and islands of mucoid connective tissue. There are cuboidal epithelial cells in masses or tubules which merge into mucoid stroma.

3. Those tumors enclosed in a connective tissue capsule with septa dividing the tumor into lobules of polygonal epithelial cells with occasional tubule formation. There is little stroma or islands of mucoid connective tissue or fat.

4. The tumors containing tubular formations of columnar epithelium and dense masses of epithelium with no keratinization. The stroma consists of septa of delicate

hyaline or mucoid connective tissue. No cartilage is present.

5. Tumors consisting of dense connective tissue with advanced hyaline degeneration and areas of calcification. In clefts in the connective tissue are clusters of small cuboidal epithelial cells with no structural arrangement.

6. Tumors with a prominent connective tissue capsule with trabeculae of hyaline connective tissue. There are masses of epithelial cells ranging from cuboidal to polyhedral at the center. These tumors contain no mucoid areas or cartilage.

7. Tumors divided by trabeculae of connective tissue and containing columnar epithelium. There are large clefts lined with cuboidal epithelium. They have no mucoid connective tissue, cartilage or stratified squamous epithelium (apparently and adenoma).

In his series, Eggers summarized the constituents of 92 mixed tumors of the palate as follows.

Mucoid connective tissue . . .		most of tumors
Gland epithelium		most of tumors
Cartilage	35	38% of tumors
Squamous epith. .	32	.34.8% of tumors

He also cites a series of 183 mixed tumors of the parotid and submaxillary glands giving their constituents as follows:

Mucoid connective tissue . .		many of tumors
Gland epithelium		many of tumors
Cartilage	78	42.6% of tumors
Squamous epith. .	56	30.5% of tumors

Wood, 1904, discusses a series of 59 mixed tumors of the salivary glands which he classifies in three groups according to their general morphology.

1. Tumors which are very fibrous and contain little cell structure, mucoid degeneration or cartilage.
2. Tumors which are very hard with much cartilage and little connective tissue or parenchyma.
3. Tumors which consist of soft, cellular mucous tissue with cellular areas and areas of fatty degeneration.

He states that tumors falling in the first two groups are usually benign while those in the third group are likely to reccur or be malignant. He discusses morphology of the tumor by grouping the types of tissue found in them.

The connective tissue is variable in appearance. If dense, it is in bands forming trabeculae with no fibrillae between the cells in the alveoli. Cells in dense connective tissue are few and normal with occasional mitoses. If soft, it is loose and edematous and often replaced by myxomatous tissue which is not always due to degeneration, but is the actual presence of myx-omatous tissue resembling embryonic tissue with long branching cells. It is often associated with cartilage so it is believed to be embryonal rather than degener-ative in character. There may be parenchyma cells scattered or in strands through the connective tissue.

Cartilage was found in one-fourth of the salivary tumors examined, but no bone was found. The cartilage is hyaline or fibro-elastic and usually the cells are normal but occasionally there are large numbers of cells together with no capsule surrounding them. The cartilage shows intimate connection with the connective tissue.

Elastic tissue is more abundant in the mixed tumor than in the sarcoma or carcinoma. It is scattered through the stroma.

Blood vessels are few and are in the connective tissue stroma. They are probably due to the normal organizing tendency of the body found in any new growth or hyperplasia.

Fat cells are occasionally seen, probably arising from embryonic tissue.

Small areas of lymphoid tissue are not uncommonly found in the mixed tumors.

The parenchyma of mixed tumors may be in the form of alveoli or solid strands. The cells in the alveoli are usually large and flat resembling epithelial cells but differing in that they have an oval, homogeneous nucleus without a nuclear network. There are seldom intercellular bridges or spines between the cells. Some areas may show cells of cuboid or polygonal shape and occasional epithelial pearls are found. The

epithelial cells have no basement membrane.

Fry, 1927, divides his series of 25 mixed tumors into two groups.

1. Those tumors with much parenchyma and scanty stroma. In the parenchyma the indefinite cell outline often gives the appearance of a syncitium. The nuclei are usually large, round or oval, with distinct nuclear markings and often a well-marked nucleolus. The cyto-plasm has no special characteristics.

2. Those tumors with abundant stroma in which the nuclei have no regular shape and size and stain deeply with haemotoxylin. The cells are triangular or spindle shape and cytoplasm extends out from the corners of the cells to blend with the stroma. The stroma consists of fine connective tissue strands which support the cells and blood vessels. In areas where cells are few there is a substance resembling mucin which stains with mucicarmine and contains fine fibrillae which stain well. In other places this substance is homogenous and takes a lighter stain. The mucin is not strictly stroma.

McFarland, 1936, states, "The immature, atypical arrangement and confused intermingling of the various tissue components easily leads to misinterpretation as to their nature and to mistakes as to their disposition."

Forman and Warren, 1918, studied seven cases of

mixed tumor and reported cartilage in three specimens. They state that osteoid tissue may be found but seldom true bone.

Patey, 1931, says the typical mixed tumor is formed of three elements: (1) collections of cells without definite arrangement; (2) adenomatous areas; (3) myxomatous areas. D'Aunoy, 1930, states that blend-ing of various tissue elements is always a character-istic feature of mixed tumors.

Hemplemann and Womack, 1942, discuss the reaction of mixed tumor tissue to stains. They state that the staining reaction differs in mucoprotein in the stromal and mesenchymal elements--the mesenchymal mucoids being nore resistant to hot dilute sulfuric acid. The mucoid in myxomatous and cartilaginous areas behaves exactly as does the chondroitin sulfuric acid complex in skeletal cartilage, chondromata, chondrosarcomata, and in the walls of arteries showing mucoid degeneration. The mucoid substance within the acini stains as does the mucoprotein complex in mucin of the salivary glands, gastro-intestinal and respiratory tracts, and mucoid carcinoma of the intestine. The conclude that there are two types of tissue in the mixed tumor.

Sheldon, 1943, summarizes the results in his study of 54 cases of mixed salivary tumor as follows: "1. The so-called mixed tumors of the salivary glands include cancerous and non-cancerous neoplasms

composed of one or two different types of neoplastic cells.

"2. Both types of cells are normally present in the salivary glands. One is represented by the secreting epithelium, the other by the basket cells. The latter are peculiar smooth muscle cells which belong to the myoepithelium.

"3. Some of these neoplasms arise from the epithelium. In these tumors an excessive and probably also qualitatively abnormal secretion produces a peculiar myxomatous and pseudo-cartilaginous appearance of the connective tissue stroma. True cartilage may be present and is formed by metaplasia from the stroma.

"4. Other neoplasms arise from both the epithelium and the basket cells. These are truly organoid tumors which closely reproduce the normal components and structures of the salivary glands. Squamous metaplasia of epithelium, myxomatous and pseudo-cartilaginous stroma and true cartilage and bone may be present.

"5. A few neoplasms arise from the basket cells alone.

"6. The presence of myoepithelial cells in these neoplasms accounts for the resemblence to tumors of the sweat glands, the mammary glands and probably also the lacrimal and ceruminous glands."

Rabillard and Chisena, 1939, describe a case of mixed tumor of the tongue in which microscopic examination showed a layer of flat epithelial cells below which were collections of hyperplastic lymphoid follicles separated by connective tissue. Beneath these was a group of glandular acini and cartilage surrounded by fibrous connective tissue. In deep portions of the tumor were areas of hemorrhage and pigmentation.

Dockerty and Mayo, 1943, divided there series of 81 cases of non-metastatic submaxillary tumors into four groups. They were: (1) The adenosarcoma mixed

tumor, five cases, with ducts and alveoli lined with two-layer epithelium and showing close attachment between gland and neoplasm. This tumor was surrounded by a thin capsule which was often invaded by tumor cells so a cleavage line was rarely found. The lack of a clean cleavage line explains the failure of eradication with simple enucleation. (2) The adenosarcoma cylindroma type, 15 cases, showing honeycombing with plugs or cylinders of small, dark staining epithelial elements in hyaline stroma. The cells are cuboidal with large hyperchromic nuclei, scanty cytoplasm and fairly abundant mitotic figures. These tumors regularly showed infiltrative tendencies, especially in the perineural lymph spaces, after removal. (3) The adenosarcoma type intermediate between the benign mixed tumor and cylindroma, seven cases, tend to lose their original mixed tumor features in recurrent lesions and behave more as a typical cylindroma. (4) Miscellaneous types, eight cases, contained no features of the benign mixed tumor or cylindroma.

CLINICAL OBSERVATION

Mixed tumors run a varied course, a characteristic quite in keeping with their other aspects. They are, however, predominantly slow growing and may be a source of interest to the patient many years before or after medical advice is sought. The majority of workers consider the mixed tumor to be a benign growth with an occasional malignancy developing after some type of violence ruptures the tumor capsule.

Harvey, Dawson, and Innes, 1938, state,

"The tumours are mainly benign, of long duration and of slow and even intermittant growth, but may, especially when internal pressure has caused rupture of the condensed fibrous capsular tissue, be locally invasive. In some of our cases the tumours were present for 20 or 30 years. Rupture of the capsule may be coincident with a history of rapid increase in size. The tumours occur mostly in association with the parotid gland, less commonly with the submaxillary and rarely with the sublingual, but they are to be found in various parts of the profacial region and arise presumably from the serous or mucous glands which are comprised under the denomination salivary."

Wood, 1904, states that the average duration of tumors in his series was about 8 years. In the pharynx the tumors were often found attached to bone. The were found along Stensen's duct, in or near the parotid or submaxillary glands, in the midline on the lip and on the anterior portion of the sternocleidomastoid muscle. They often appeared to be fixed due to stretching of the capsule rather than from invasion. Usually they were movable as was the skin overlying the tumor.

Eggers, 1928, states that mixed tumors of the palate are almost all malignant according to morphology but practically none are malignant clinically. Fry, 1927, observes that in his series of 25 tumors there was usually a long period between the first appearance of the tumor and the time of treatment. The period was more than 5 years in all but three cases, and in two cases this period was 26 and 27 years respectively. Characteristically, the tumor remains more or less stationary for many years and then suddenly grows rapidly with no apparent cause. In some cases the patient would attribute the rapid growth to some blow or injury.

Freedman, 1926, states that mixed tumors of the parotid may migrate to the inner side of the lower jaw and come to lie inside the oral cavity. Bland-Sutton, 1922, says salivary tumors may dip beneath the sterno-cleidomastoid muscle and infiltrate the sheath of the carotid artery and jugular vein. Left to themselves, parotid tumors may cause death in a variety of ways. They may press on the pharynx and interfere with swallow-ing, or they may ulcerate and open large vessels in the neck and lead to death from bleeding, sepsis, and infection of lymphatics. They may require 10 to 12 years to reach the size of a hen's egg and have run as high as 44 years, reached enormous size, and still

been successfully removed. Keen, 1904, observed one of the largest mixed tumors of the parotid which have been reported, the specimen weighing seven pounds.

Wilson and Willis, 1912, in their analysis of 56 mixed salivary tumors give the duration of tumors before operation as ranging from one month to 44 years, most ran between one and ten years while the average was six years and four months. They state that there is no relation between mumps and tumor formation. They group their tumors according to gross appearance as follows:

(1) Hard, fibrous with little cartilage or parenchyma (15 cases).

(2) Very hard with much cartilage (17 cases).

(3) Soft, sarcoma-like with little connective tissue and much parenchyma (20 cases).

(4) Grossly resembling carcinoma (4 cases).

Patey, 1931, divides his series of 55 tumors into two main types--(1) A soft, highly cellular tumor liable to recur after operation (2) A harder, acellular, fibrous tumor, operative removal of which will probably be followed by prolonged freedom from recurrence.

D'Aunoy, 1930, says, "Microscopically complex, but clinically benign, it is doubtful if typical mixed tumors ever undergo so-called malignant changes. Certainly such transformation, if occuring, are diffi-cult of proof."

McFarland, 1936, states that the average mixed tumor grows regularly and slowly so as to attain the size of an orange or grapefruit in 20 years, all the time remaining localized. There are no metastases or complications unless trauma produces ulceration, hemorrhage or infection. Prompt surgical intervention is not necessary--wait until the tumor is "ripe", the size of a lemon or larger. Smaller tumors recur twice as often probably because small lobules are overlooked which would later be included in the growing mass. If malignancy is suspected due to rapid growth, surgery probably will not do much good anyway. No microscopic structure serves in the prognosis. One cannot say whether mixed tumors are predominantly benign or malignant. If undisturbed, the tumor may simply become larger. The largest tumor in McFarland's series weighed 11⅛ pounds. The largest tumor on record, Contrill's case, weighed 26 pounds. Mixed tumors of the salivary glands are among those most prone to behave in an unexpected manner. They are inherently benign, but commonly recur after excision and if frequently disturbed become locally destructive and invasive without giving metastases. The rapid enlargement of a mixed tumor of long duration and slow growth is not the result of malignant change, and such changes must be very rare and their occurrence difficult to prove.

Neely, 1937, describes the development of a typical lacrimal gland mixed tumor as slow with the eyeball being gradually pushed nasally. There is limitation of upward and outward motion of the eyeball, and lacrimation and exophthalmos are common although there is seldom any pain. Proptosis is the rule in later stages and impaired vision is common.

Ziporhes, 1937, reported a case of lacrimal gland mixed tumor in a woman 40 years old. The patient noticed ptosis of the right eye for seven months with tearing and blurred vision for three months. There was limited upward and outward motion and diplopia. Surgery cleared up the case and vision returned to normal.

Patey, 1940, states that the natural cause of a mixed tumor which the patient and doctor may anticipate, if no active treatment is started, is a gradual increase in size of the tumor. In one case this may be so slow that after 30 years the deformity is negligible, and in another case may result in unsightly deformity in a few years. Widespread infiltration is frequently seen but there is little tendency for skin ulceration regardless of size of the tumor, and there is rarely pain.

Smith, 1939, discusses a case of mixed tumor of the right sublingual gland in a 31 year old woman. It had been present for 17 years and although there were pulmonary metastases, there was no demonstrable lymph node involvement.

Brunschwig, 1930, reports on a case of malignant mixed tumor or cylindroma which was present for 19 years. This tumor was apparently benign at first but finally became malignant causing extensive local destruction and producing metastases in the lungs and pleura. He also repotts a case of slowly growing malignant mixed tumor of the tongue of several years duration with metastases to regional lymph nodes. Combined surgery and radium therapy appeared to have eradicated this process.

Rabillard and Chisena, 1939, report a case of mixed tumor of the tongue which persisted as a small mass the size of a pea on the left border one inch from the tip of the tongue. It was removed and there was no evidence of recurrence or regional metastasis. They report that such tumors are rare and seldom malignant. They do not grow rapidly and produce only regional metastases when malignant.

Parrin, 1942, presents a case of mixed tumor of the parotid with distant metastases which were discovered shortly after removal of the primary tumors and histologieally diagnosed as mixed tumor of salivary gland type. These metastases were found in the lungs, liver, retroperitoneal tissue, subcutaneous tissue, omentum and vertebrae. The clinical course showed and increase in metastases over a seven year period.

Dockerty and Mayo, 1943, state that in their series of 81 tumors, 63 per cent were benign, 18.5 per cent were the cylindroma or malignant type, and 9.9 per cent were atypical. The average duration of the benign mixed tumor was seven years with recurrence, if any, in 4.7 years. The average duration of the cylindroma type was three years. Pain or tenderness was rare in the benign type. In the cylindroma type, however, eleven of fifteen patients complained of stabbing pain in the tumor region due to fixation and nerve involvement--a good differential diagnosis in the benign and cylindroma types. They recorded no direct death due to the benign mixed tumor while there was a 50 per cent mortality with the cylindroma.

McFarland, 1943, says that infiltrative growth is rare in mixed tumors which all have a capsule. Local tissue destruction is rare except from pressure on the skin, and toxic products from the uncomplicated tumor are doubtful unless one gets ulceration, bleeding or infection. There may be local interference with function such as in jaw maovement or facial nerve palsy, pain or tic douloureux. Recurrences are hard to evaluate since the patient must be followed 25 to 30 years before a definite statement can be made. In 100 cases studied, two patients showed lesions which looked like metastases but the patients lived five and twenty years respectively after the appearance of the lesions.

Fox, 1939, describes a mixed tumor of the salivary gland type in the pharynx. On inspection one observes a fulness or swelling of the neck below the jaw and mastoid process, over the angle and adjacent surface of the mandible and parotid region anterior to the ear. There is no inflamation of the skin. The pharynx has a smooth medial bulging of the lateral wall which early resembles an enlarged tonsil. As the tumor enlarges, the tonsils are crowded postero-inferior to the base of the tongue and nearly obscurred. As the soft palate is invaded, it bulges down and medial so soon there is no distinction between the pharyngeal wall and soft palate. The tumor pushes past the midline carrying the edematous and enlarged uvula along. The mass is smooth, glistening and rounded and covered by indistinct and thin mucus membrane and pharyngeal muscles. There is no ulceration, inflamation of congestion of vessels. The pharyngeal and nasopharyngeal orifices are diminished but there is not much embarrassment to swallowing or breathing.

Rosedale, 1943, discusses a case of mixed tumor of the palate in a 63 year old woman, who 22 years previous had noticed a small swelling in the roof of the mouth. When examined, this swelling was the size of a hen's egg in the hard and soft palate to the left of the midline. Removal of the mass measuring 3.5 x 4 x 2 cm. resulted in an uneventful recovery.

Rosedale states that palate tumors are encapsulated, rubbery in consistency and resilient. They are lobulated, of a greyish-yellow color and smaller than those found in the parotid gland.

TREATMENT

Every aspect of mixed tumors has aroused controversy among the workers in this field and their treatment is no exception. Some men advocate simple enucleation, others suggest removal of tumor and surrounding tissue, others believe incomplete removal and implanting radium at the tumor site is adequate therapy. X-ray has been advocated as both pre-operative and post-operative therapy, and is, of course, universally recognized as the most successful treatment in metastatic lesions. As a result of the unpredictable progress in these tumors, probably all of the above-mentioned procedures have met with success or failure at various times, and there is no completely standardized treatment at present.

Dockerty and Mayo, 1943, state that frequently when a true mixed tumor of the salivary glands exists, complete removal of the growth and capsule gives a cure just as does removal of a low grade malignant growth encapsulated in an adenoma of the thyroid. Cure is as permanent as when a benign lesion is removed. The type of malignancy is determined by pathological means. It is essential to perform more radical operations when dealing with a cylindroma type of malignant lesion of the salivary glands because of the invasive characteristics on which the high rate of recurrence of residual

growth is dependent. Mayo recommends in diagnosed malignant tendency that radical operation with removal of the facial capsule, Stensen's duct and adjacent suspicious tissue besides the gland itself be performed. Additional block gland dissection of the affected side of the neck is neither recommended nor condemned. Care must be exercized to prevent injury to the marginal mandibular branch of the facial, the lingual and the hypoglossal nerves. It is more difficult to remove parotid tumors than those of the submaxillary gland, so there are more recurrences from tissue left behind. They emphasize that the tumorsshould be completely removed en bloc and not shelled out.

Fox, 1939, reporting on a mixed tumor in the pharynx, states that it was removed through an intra-pharyngeal incision. He concludes that biopsy of such tumors is contra-indicated because it breaks the capsule. He believes the capsule should be present to prevent leaving any tissue behind.

Patey, 1940, claims that surgery in mixed tumors of the parotid gland may either cure or kill with recurrence and widespread infiltration, but he further states that radical removal of the tumor and surrounding tissue is probably the safest procedure. He concludes that enucleation followed by irradiation is on present evidence the best treatment for mixed parotid tumors.

Woodson, 1942, maintains that blunt dissection is the best method of removing mixed tumors from the pharyngomaxillary space. He advises against biopsy as this breaks the capsule and scarring makes removal more difficult. He further states that radium and x-ray therapy are no good because the cells are not radio-sensitive.

McFarland, 1943, emphasizes the fact that one should not excise a mixed tumor immediately if there is no emergency or definite indication, but should wait until the tumor is larger or "ripe". He bases this therapy on the belief that if a small tumor is removed, the surgeon is liable to miss small lobules of tumor tissue which would later be incorporated in the main tumor mass as it increases in size. Patey, 1941, however, suggests that the drawback to this expectant treatment is the inability to differentiate a mixed tumor and adenolymphoma by microscopic examination, and x-ray therapy must be used for diagnosis of adenolymphoma. He states that radium and x-ray therapy alone are not satisfactory in mixed tumor treatment since most tumors are radio-resistant and show only negligible decrease in size. Fitzwilliams, 1935, states that heavy doses of buried radium after surgery almost abolishes the risk of recurrence. Hybbinette, 1935, claims that pre-operative irradiation toughens the tumor capsule and makes surgery more certain.

Ahlbom, 1935, gives a series of 90 benign mixed tumors treated with x-ray. Of these, 85 were free of symptons after two to twenty-one years, and the five with recurrences were also successfully treated with irradiation. Fox, 1930, however, maintains that local application of radium or x-ray alone is no good in treating mixed tumors. Dockerty and Mayo, 1943, suggest making a microscopic diagnosis before using irradiation, and in diagnosed cylindroma use intensive x-ray therapy after surgery. As yet they have no statistics on such therapy. Popp also recommends pre- and post-operative radiation therapy in salivary gland tumors if they have been diagnosed as milgnant. Such treatment, however, will make removal of recurrences in the benign tumors difficult or impossible.

Smith, 1939, reports a case of mixed tumor of the sublingual gland with metastases in the lungs in which the local growth was restricted for six years by x-ray therapy, and the patient was alive 17 years after the tumor was first noticed.

Levin, 1940, concludes, that in view of its derivation, the mixed tumor must be radio-sensitive, and he gets confirmatory results clinically. He states that, because of its slow growth, intensive therapy is unnecessary, and there is not much surrounding tissue destruction so radium can be continued for recurrences.

Levin's therapy consists of incomplete excision of the tumor accompanied immediately by insertion of radon capillaries, 4 to 8, each having 1 m. c., into the operative field. The site is then closed and subsequently aided by surface application of small blocks of radium consisting of about 100 mc. hours for each treatment. He admits that as yet one cannot consider the ultimate results of such therapy and set a limit of years. One case recurred 11 years after beginning treatment, and another, autopsied 11 months after beginning therapy, showed no tumor tissue. With few exceptions, in the cases studied, the tumors shrank promptly after treatment.

Patey, 1931, concludes that surgery plus radium, or in infilltrative cases radium alone, may hold the mixed tumor in check for sometime. Quick, 1923, claims the more cellular types of mixed tumor responds better to radium while the acellular, myxomatous types are resistant.

Rhoades and Mecroy, 1937, believe there is little use for irradiation in mixed tumors and surgery is the best treatment. They use post-operative irradiation when the capsule is broken in the hope of preventing recurrence. Hocke and his co-workers, 1935, state that mixed tumors of the lacrimal gland are absolutely refractory to radio-therapy and advise only surgery.

PROGNOSIS

The course and prognosis of mixed tumors is unpredictable. The large majority are benign and once removed apparently give no more symptons. There are, however, many reports of recurrences taking place a number of years afterwards, so a patient must be followed for a long time before anything but a guarded prognosis can be given. The variability of the microscopic structure of the tumor makes prognosis on a pathological basis uncertain except in those cases where a rank malignancy may be demonstrated.

McFarland, 1936, has very definite ideas regarding prognosis in mixed tumors. He states that mixed tumors of the salivary glands are among those most prone to behave in an unexpected manner. They are inherently benign, but commonly recur after excision, and if frequently disturbed become locally destructive and invasive without giving metastases. Histological variation has no bearing upon prognosis, and the microscope, beyond showing that the lesion is a mixed tumor, is misleading. The rapid enlargement of a tumor of long duration and slow growth is not the result of malignant change. Such malignant changes must be very rare and their occurrence difficult to prove since most tumors are malignant in themselves and not by virtue of any "sarcomatous" or "carcinomatous" degeneration. Except

in rarest cases there is no metastasis, so that the type of malignancy is peculiar.

The mixed tumors have a fairly regular rate of growth that is ordinarily very slow. McFarland states, "When growth is so rapid as to bring the patient to operation within a year, and the excised tissue resembles carcinoma, the prognosis is bad." The age of the individual at the appearance of the tumor is not significant as far as a malignancy is concerned. McFarland cites a series of 297 mixed tumors of which 69 (23.23%) recurred and 13 proved fatal. Of this series, 278 were in the parotid gland of which 60 (21%) recurred, 22 in the submaxillary gland of which 8 (36%) recurred, and one in the sublingual gland which also recurred. Promptness of recurrence, however, is no indication of future behavior, and recurrence takes place at any time from "immediately" up to 47 years after operation, so it is impossible to prove that any case has been cured or that any kind of treatment is certain in its results.

Freedman, 1926, concludes that although the mixed tumor is of slow growth, does not invade regional lymph nodes, or metastisize at a distance, yet it is advisable to follow up even total removal of the tumor by the application of the gamma rays of radium to prevent the 45 per cent possibility of local recurrence.

Lane, 1922, reviewed the literature on lacrimal gland tumors and states that in the series which she

studied, there was a recurrence in 20 percent and a mortality of 12.6 percent.

Bland-Sutton, 1922, states that a tumor may arise in a gland and grow to the size of a walnut and remain stationary for 10, 15 or 20 years, then, without warning, it enlarges, infiltrates the gland, causes pain and kills the patient in a few months. In another person, a tumor arises, grows quickly, ulcerates, and causes death in nine months. The microscopic features in each case may be similar.

Patey, 1931, gives the main causes of recurrence in mixed tumors after operation. They are (1) failure to remove all of the tumor (2) multiple tumors (3) tendency in the gland to produce tumors. He states that there is no more malignancy in recurrent tumors than in the primary growth.

Wood, 1904, divides his series of 59 mixed tumors according to prognosis as 25 per cent malignant, 30 per cent recurrent, 55 per cent cured by excision. He gives no explanation for malignant change but suggests the possible irritation by muscles of mastication. The original growths have a dense capsule and poor blood supply. If some tumor tissue is left after surgery, however, there may soon develop a larger tumor than the original. Occasionally the tumor may invade blood vessels of the neck and emboli may be carried through the body.

Bilroth reports a case which ran 23 years and required 9 operations to remove local recurrences.

Eggers, 1928, states that malignancy in palate tumors is rarer than in the salivary glands, usually only when trauma allows escape from the capsule. Palate tumors are usually removed earlier due to the production of obstruction.

Harvey, Dawson, and Innes, 1938, state that clinical malignancy is extremely rare in the sense of metastasis to lymph nodes or distant parts. On the other hand, recurrence is common with involvement of neighboring tissues. Where mastication and deglutition are interfered with by huge growths, death may result from malnutrition or from sepsis.

Wilson and Willis, 1912, conclude that grossly hard tumors consisting of fibrous connective tissue or cartilage are proliferating at their periphery only and are usually benign. The grossly soft tumors, however, are mostly parenchyma of adult or embryonic type and are the tumors which become malignant.

D'Aunoy, 1930, states, "Microscopically complex, but clinically benign, it is doubtful if typical mixed tumors ever undergo so-called malignant changes. Certainly such transformations, if occurring, are difficult of proof."

Parrin, 1942, discusses a case of mixed tumor of the parotid where metastases were found. He states that

these metastases were not due to surgical trauma but preceded surgery. He adds that the metastatic lesions showed no carcinomatous or sarcomatous degeneration had taken place before or during development of metastases.

Hudson, Smith, and Smith, 1942, describe the clinical and pathological aspects of two salivary gland tumors arising in the floor of the mouth. In one of them microscopical evidence is given of spheroidal-cell carcinoma arising in a typical mixed tumor and in the other there is evidence strongly suggesting a similar change.

Olson, 1937, reports three cases of pulmonary metastases from mixed tumors. One patient, a 49 year old woman, had a tumor for 14 years which had been incised twice, excised and radiation applied. The patient died with pulmonary lesions which had completely replaced the right lung and four-fifths of the left lung. Another patient, a 48 year old man, had a lump on the throat for one month which was treated with two operations and 400 mgm-hours of radium, but a year later the patient died with pulmonary metastases. The third patient was a 59 year old man who had noticed a lump on his right jaw which persisted for two years. The tumor was removed and x-ray applied, but a year later a lump appeared on the sternum which was diagnosed as

a metastatic lesion. Similar lesions were found in the lungs and treated with radiation. Olson believes many patients with mixed tumors die at home of pulmonary tuberculosis which might prove to be mixed tumor metastases if the patient were autopsied. He feels that routine Roentgen studies of the chest should be made before therapeutic measures are undertaken for mixed tumors.

Mulligan, 1943, reviews 20 cases of mixed salivary tumors which showed metastases. He states that in 19 cases the duration of the tumor before the patient was first seen ranged from two months to 19 years. In eleven cases the size ranged from an olive to half of the head. Duration of life in 17 cases was from two days to 13 years. In this series metastases were found in the lungs in 18 cases, pleurae in 12 cases, liver in 10 cases, bones in 8 cases, lymph nodes in 6 cases, kidneys in 3 cases, and spleen in 2 cases. In this series eight cases were called "cylindroma", five cases "mixed tumor", two cases "adenocarcinoma", one case "malignant glandular epithelioma", and one case "alveolar sarcoma".

Ahlbom, 1935, after analysis of a large series of cases, states that at the Radiumhemmet they have never seen a histologically benign salivary tumor become malignant.

Patey, 1940, states that in mixed tumors, even surgery followed by irradiation does not insure against recurrences although it is probably advantageous.

Harris and Schattenberg, 1942, claim that tumors of embryonal origin tend to be more benign than those of primary nature which may aid in the prognosis of mixed tumors.

Fox, 1939, concludes that in treatment of mixed tumors by surgery, there is little post-operative reaction;recovery is rapid and function is soon restored. claims there is little recurrence if all tumor tissue is removed.

McFarland, 1942, states that something more than a simple microscopic section examination of tissue will be required before an accurate prognosis can be made on mixed tumors of the salivary glands. An exper-iment in which 50 slides were given to 25 competent microscopists to prognosticate as to recurrence gave an average of 52 per cent correct and 48 per cent wrong. He states, "At present, our methods are no more accurate or scientific than the flipping a coin."

ORIGIN

When one speaks of origin or cause of any neoplastic process, he travels in the realm of speculation rather than fact. The development of single-tissue tumors is still a controversial subject as regards predisposition and direct cause. It is no wonder, therefore, that the mixed tumor, in which even the types of tissue found are contested, is the source of much controversy.

Several theories regarding the origin of mixed tumors have been advanced by workers in the field, and all have their strong and weak points, but none have been proven conclusively. Among these theories might be mentioned the following: (1) Embryonic displacement (2) Endothelial derivation (3) Epithelial derivation (4) Branchial derivation (5) Embryonic gland germs. Since most workers subscribe to one of the above-mentioned theories of origin, it is convenient to group the evidence of each under the theory which he supports.

The endothelial derivation theory does not have many converts. Martini,1907, concluded that the presence of fibrous connective tissue in the youngest parts of a tumor and of myxomatous and cartilaginous tissue in the older parts indicated that these varieties of connective tissue are the product of metaplasia of the fibrous stroma and not the product of germi-

aberrantes or other mesenchymal elements, although their origin is still undecided. Martini could not identify true gland tissue in his specimens and asserts that the "acini" lack a limiting membrane and the supposed epithelial cells are intimately related to the stroma. He feels that he can trace the origin of the tubules and cell formations from proliferating endothelium in the lymph vessels.

Von Hansemann, 1910 , studied one enchondroma of the parotid in which he thinks he can trace the development of the parts from a lymphangioma. He says,

"I consider in fact this tumor a lucky finding which makes it possible to advance the sureness of the endothelial nature of the so-called parotid enchondromas. That lymphangiomas are present in the parotid has been long established. That, up to this time, such characteristic stages as are present in the tumors in question were not found is because these tumors were only seldom studied in the initial stages."

Eggers, 1928, states that the endothelial derivation of the mixed tumor is contradicted by the definite glandular structures found in these tumors.

Fraser, 1918, states,

"The endothelial theory has no foundation in fact. All the so-called endothelial structures are easily explained as natural modifications of primary duct formations. The most common one, viz., the peritheliomatous formation, is a figment without histological basis for it is now generally agreed among histologists that the perivascular lymph space from the endothelium of which it is supposed to arise, is not a lymph space lined with endothelium, but merely a tissue space to facilitate the expansion and contraction of the vessel."

The embryological theory of origin of tumors is popular because it allows an explanation of any condition found in tumors. It is especially helpful in considering mixed tumors where it is difficult to explain the presence of various mixtures of tissues. With this theory the totipotential embryonic cell assumes the responsibility for anything that develops, and removes the burden of proof from the exponents of t theory. However, embryonic rests, the basis of the explanation, have not been proven conclusively to be the cause of any tumor, and experimental data in this field is lacking.

Fraser, 1918, states, "Undoubtedly, many of the histological phenomena in these tumors look odd and at first sight, puzzling, and, as is our custom when thus puzzled, we are inclined to seek refuge in the embryonic realm. I have frequently shown sections of these tumors to experienced embryologists, but none of them seemed to recognize in them any structure with which he was familiar."

The main point of confusion in most mixed tumors is the fact that they contain both cartilage and epithelial structures. Since cartilage is considered a derivative of mesoderm, and epithelium is of ectodermal derivation, an explanation requires the assumption of one of three theories. They are:

1. Embryonic rests of totipotent cells or containing more than one embryonic tissue.

2. Metaplasia of tissue.

3. Either the cartilage of epithelium is not a true structure.

Wood, 1904, states that tumors tend to predominate in regions which contain complex organs of mesoblastic origin and complicated development such as the face, kidney, ovary, testicle, and posterior gut. In these regions early mesoblastic origin leaves cells with all possibilities and they are often associated with developmental defects.

Klebs and Ortho think that cells have specific stability and cartilage comes only from embryonic tissue. Virchow believed that cartilage was derived from connective tissue, while Cohnheim thought is arose from the branchial arches.

Wood says,

"Inasmuch as the arches reach there development at about the fourth week, and at that time contain the cartilaginous tissue which forms Meckel's and Reichert's cartilages, while the parotid does not appear until the sixth or eighth week, for any embryonic remnant to contain both parotid and cartilage, the tissue must have been displaced before the fourth week. It is not, therefore, a portion of parotid tissue which is displaced, but a portion of the epiblast which is to line the buccal cavity together with some of the underlying mesoblast, the latter carrying with it the whole group of mesoblastic possibilities--cartilage, myxomatous tissue, fat, and even muscle. This necessarily early displacement of the tissues would make up the tumor accounts for the great variability of the mesoblastic and epiblastic structures present in the growth and the close intermingling of cartilage, myxomatous tissue, hyaline, fat, muscle, and bone, together with cells of

both epithelial and connective tissue types. This theory makes the assumption of Hinsberg of metaplasia to form epithelium, unnecessary.

"The problem of the exact nature of these growths cannot be definitely settled so long as we must rest our distinctions upon morphological or histogenic differences."

He concludes,

"The complicated structure of the stroma containing as it does elements such as embryonic connective tissue, cartilage, bone, fat, lymphoid tissue and very rarely striated muscle is explained most easily by the assumption of an embryonic misplacement of mesoblast.

"The structure of the parenchyma is so slightly characteristic in morphology that its epithelial nature in all cases can only be considered as probable; yet in about 24 per cent of the tumors examined the presence of epithelium is undoubted. The form and relationship of the cells of the parenchyma do not furnish sufficient data to justify these cells being regarded as of endothelial origin.

"The theory of early embryonic displacement of epiblastic tissue during the process of formation of the parotid and submaxillary glands and the branchial arches may account for many of the morphological peculiarities of the cells of these tumors, especially the lack of many typical features which we associate with epithelium. The same condition may be seen in the epithelial cells of the congenital moles, in which the epithelium is with difficulty distinguished from connective tissue cells, owing to its close connection with the stroma of the tumor and its undifferentiated type."

Eggers, 1928, compared 92 palatal to 183 parotid and submaxillary tumors and demonstrated less cartilage and more stratified squamous epithelium in the palatal tumors. He states that this is to be expected if the displacement theory is correct in view of later development of the palate. The embryonic displacement theory usually holds good except when the tumor tissue blends

with the normal gland structures.

Fox, 1939, concludes that the most acceptable theory of origin of mixed tumors is that they spring from cells that became isolated from normal groups of cells during the embryonic period and remain dormant during the body development. Later they are activated and become tumors. They are isolated after differentiation of the advanced embryonic stage so they resemble adult tissue and are not usually malignant.

Freedman, 1926, believes mixed tumors arise from misplaced embryonic mesoblast and epiblast rather than from metaplasia. The occasional migration of a tumor to the inner side of the jaw may be explained by the persistence of aberrant embryonic sprouts from the primitive parotid tube.

MacCallum, 1936, believes any malignancy in mixed tumors is due to a few embryonic or chorionic cells included in the rest which give metastases.

Verhoeff, 1904, concludes that mixed tumors are essentially epiblastic in origin. The stroma of these tumors is not derived from mesoblastic cells misplaced from other structures, but is probably produced by an atypical development of cells which ordinarily would have gone to form part of the stroma of the normal gland.

Massabuau, 1907, states,

"The theory which explains in a perfect manner the

structures of these mixed tumors of the salivary gland is that which explains their development from ecto-mesodermic rests of the embryonic bud which was destined to the formation of the glands themselves. (1) It is the one important fact in the development of the mixed tumors on the border of glandular organs. (2) It explains the new formation of the flat epithelium as well as the normal and edematous glandular epithelium. . . . (3) It explains perfectly the intrication of the two orders of endothelial proliferation. . . (4) There is no need for invoking, as in the endothelial theory, a cellular metaplasia for explaining the development of the polymorphoric connective stroma of these tumors."

Wilson and Willis, 1912, state that in mixed tumors both connective tissue and parenchyma tend to revert to embryonic type, and there is little evidence that they arise from adult epithelium or endothelium but are probably mesotheliomas of embryonic origin.

Goldsmith and Ireland, 1936, reported on six mixed tumors in the nose and throat. They state ,

"The general consensus of opinion is that these tumors are not true teretoma. Those closely associated with the glands proper probably arise from the gland ducts and the aberrant type from embryonal rests. Cartilage and myxomatous tissue can be developed by metaplasia and their mesodermal origin is not considered essential."

Neely, 1937, in discussing mixed tumors of the lacrimal gland states that correlation of histology of the tumor with development of the lacrimal gland strongly supports the theory that these tumors are developmental, representing misplaced embryonic rests or enclavements. Study denies transition between epithelium and mesenchymal elements of the tumor, and demonstrates that both the epithelium and mesenchyma take an active part in tumor growth. Occasionally a basement membrane is encountered.

The big problem confronting the exponents of the epithelial derivation theory is the explanation of cartilage in the salivary mixed tumors. Some workers maintain that cartilage can be derived from epithelium, others suggest a stimulating action of the tumor on connective tissue, while some avoid the problem by denying the existence of true cartilage in mixed tumors. They maintain that it is merely a degeneration product of the tumor tissue.

Boyd, 1938, suggested that cartilage in the tumors was merely a homogenous myxomatous material secreted by epithelial cells and resembling cartilage in appearance and staining properties.

Bland-Sutton, 1922, states that parotid cartilage resembles immature cartilage. Gaskell studied chondral tissue of the lamprey and ammocoete and found that cartilage of the branchial bars differs in histology, staining reaction, and chemical constitution from hyaline cartilage. It is called muco-cartilage while skeletal cartilage is called hard cartilage. The tumor tissue resembles muco-cartilage and Bland-Sutton concludes, "A critical consideration of histological features of the t sue called cartilage in parotid tumors convinces me that it is not entitled to this distinction."

Micholson, 1922, in his discussion on tumor formation, states that he has seen cartilage with and

without perichondrium in three cases of tonsils. This was associated with chronic inflamation, hyperplasia and fibrosis of the capsule while the cells in the center were gradually converted to cartilage cells. In one case a fibrous band contained minute lobules of adipose tissue around one of which conversion of fibroblasts into young cartilage cells was taking place. This seemed to be clear evidence of its origin *in situ* as the result of fibrosis. The fact that the nodules were scattered in all parts of the capsule supports this view. This tissue has been found in a variety of inflamatory conditions in which it is frequently associated with bone and is often recorded in sclerotic arteries. Nicholson believes that the formation of cartilage in the living tissue is occasionally the end result of a mucoid degeneration.

Marburg, 1902, has described an arteritis carti-laginosa of the cerebral vessels which appears to re-sult from mucoid degeneration of their stroma.

Patey, 1931, concludes that the controversial tissue either is not cartilage or else it is and, as such, is derived from epithelium by metaplasia. He thinks this is not impossible since cartilage and myxomatous tissue are closely related, so an occasional area resembling cartilage is no objection to the epithelial nature of mixed tumors.

D'Aunoy, 1930, states that it is now generally believed that the mixed tumor is of epithelial derivation with metaplasia giving stromal tissue. He sheds is generally conceded a developmental relation between tumor and embryonal disturbances in nature of cell displacements or enclavements. The tumor should be regarded as a tumor in, but not of, the structures which it invades.

Harvey, Dawson, and Innes, 1938, state in regard to cartilage found in mixed tumors,

> It may now, however, be justifiably contended that it is not cartilage but pseudo-cartilage or a myxo-chondroid substance developed from epithelium and stroma by a transformation which we must regard as a degeneration, possibly combined with a manifestation of the secretory function of the tumor cells. The substance developed is of the nature of mucin, a conjugate protein, or one of its allies, pseudomucin, 'mucoid', or chondroprotein. Individual epithelial cells which have not quite disappeared into the acell-ular, fibrillar, or homogenous mucoid material tend to be isolated in a retraction space which gives them all the appearance of cartilage cells within their capsules, especially as the margins of the containing spaces stain somewhat deeply. supporting tissue of the tumour may be of ordinary fibrous connective tissue type and may contain groups of fat cells, but is usually myxoid, whether by inhibition of the epithelial mucinous product or by an autogenous metamorphosis. In this process epithelial and connective tissue merge one into the other and may lose almost all indication of their usual delimatation borders, the epithelial cells being disseminated singly or in groups in the mucoid matrix. Staining reactions of this matrix vary, but are usually metachromatic. It must be contended here, however, that the stains thionin blue, toluidin blue and mucicarmin, which are used to pick out mucin, are probably only partially specific. We find, too, that hyaline staining may also be a marked feature of these tumours; they have indeed been called muco-hyaline carcinomas. It seems probable that hyaline and mucoid changes are only phases of the same process and that the two types of stroma may merge into one another.

"As regards the nature of these "mixed tumors", discussion by pathologists has swung from a connective tissue to a purely epithelial and, for a time at least, to an endothelial composition. They have been regarded as tumours of either glandular or branchiogenic origin. One criticism of the view that the tumours are essentially adenomas is the the tumour appears very constantly walled off from normal gland by a dense fibrous tissue. Our preparations, however, give indications that, in some cases, there is continuity between gland and tumour, and it is said that this continuity can be quite frequently made out somewhere if serial sections are cut. Tumours of the parotid resemble the basal-cell carcinoma of the skin. Here it may be well to recall that these skin tumours, just as the parotid tumours, have their adenoid and adenoid cystic, as well as their epidermoid types. When, therefore, the basal-cell carcinoma, the 'cylindroma', and the 'benign cystic epithelioma' occur in the parotid without any definite genetic relationship to the epidermis, we propose to call them salivary gland adenomas. . . When salivary gland tumors are malignant, even when they show epidermoid character, they are s ivary gland adenocarcinomas.

"The favorite belief hitherto regarding salivary gland tumours seems to have been that they were 'enclavomas' or branchiomas in the Cohnheim sense--bidermal fibroepithelial tumours. While the close relationship in which the parotid and submaxillary glands are placed to the first and second branchial arches in embryological development would favor this conception of a teratoid constitution it would not easily account for the 'mixed tumours' of lip, palate, nose, etc. It seems however, only necessary to return to the original Cohnheim conception of a residual embryonal foundation representing the original embryonal production of cells in excess of immediate local structural requirements, to find all that is needed in explanation of these tumours and make them gland-lobular instead of bidermal. should not in our conception of tumour development anywhere, lay stress solely on the excessive production of the cells of a primordium, for it requires only a slight modification of the theory to extend the conception of tumour production to a normally persistent rather than a residual embryonal cell. The cell concerned becomes then the seed, stem, or replacement cell of all normal adult tissue, while benign and malignant tumours may be pictured as arising only in these embryonal cells and never in adult differentiated cells. Such a theory still finds

room for the conception of a residual and therefore excessive debris of cells and cell groups, describable as a dysontogenetic field or malformation as the source of tumour growth. The branchiogenic or fetal fissure origin of salivary gland tumours was almost a necessity as an explanation of the cartilage supposed to be characteristically present in them. Uncertainty also regarding the exact nature and importance of the component tissues of the 'enclavoma' necessitated the use of compound descriptive titles such as myxo-chondro-fibro adenoma or carcinoma. Removal of the stumbling block of associated cartilage with epithelium in these 'mixed' salivary gland tumours by denying it to be true cartilage and regarding it as a degenerative transformation of epithelium and stroma sweeps away much of the difficulty in considering them as salivary gland epithelial tumours with lobular stroma. In this we return to what was an early tenet, one which has always been vigorously held, what we may call the gland-lobular view. We have thus to do with an adenoma, similar to the gland-lobular adenoma of the breast. The latter tumour commonly makes its appearance before the pathologist with a preponderance of the fibrous element of the gland-lobule and receives the name of 'fibro-adenoma', but not, as a rule, 'mixed tumour' of the breast. Moreover, myxoid change is very frequent in it. There may even be development of true cartilage or bone, especially in tumors found in dogs' mamma. Cartilage and bone in such cases are usually regarded as metaplasia in mesodermic tissue. Any inclination to resort to an explanation by way of ectodermic epithelial production of cartilage, such as apparently seems to happen in some lowly animals, we think, may be discouraged.

"The mucoid changes in salivary adenomas is very striking. The 'colloid' carcinoma, the myxoma and the 'mixed' tumours may all represent something of a similar disintegration change, a suicidal autolytic, cytolytic process. It occurs to use that the transformation may have some anology or even identity with the suicidal colony of bacteria, which disappears by autolysis or 'bacteriophage', in a viscous mucinous mass.

"To sum up: We regard the 'mixed tumour' of salivary glands as arising in embryonal glandular, replacement epithelium, whether sequestered or non-sequestered. Proliferation slowly takes place in this epithelium and its stroma for the same reason as in any benign tumour or even simple malformation. The proliferation of the stem cells may be anaplastic,

metaplastic, or differentiated to an organoid glandular character. A special proneness to auto-destruction of parenchyma and stroma is a feature of the tumour and this may have some relation to the type of secretion proper to the gland affected."

Fry, 1927, states that the so-called mixed tumors are not in reality mixed but are entirely epithelial in origin. They are in most cases derived from the ducts of the glands, but occasionally arise from the secretory cells. It is believed that the ducts are the source of origin since the cells contain no zymogen granules which are present in gland tissue proper. He states that cartilage in mixed tumors is really mucin secreted by cells since it stains with mucicarmine as do granules in the cells. The capsule around the cell is really strands of mucin which stains darker than the homogenous structure outside. There are occasionally mucin secreting cells in ducts of normal glands, so the mucin in the tumors is just the result of an exaggeration of a normal function of the epithelial cells.

Fraser, 1918, believes mixed tumors arise from the ducts of adult glands. He makes no claim that true neoplasms have been produced experimentally but results do support this theory. Injury such as localized or partial obstruction of ducts probably plays a prominent part in the origin of these tumors. Fraser states

"The cartilage is developed from the epithelium of the parenchyma of the tumor. This claim will undoubtedly

meet with strong opposition, but I am compelled to let the facts stand as above reported."

Pilcher, 1937, states that mixed tumors of the lip are generally thought to originate in the labial glands in the lateral portions of the submucosa of the upper lip.

Hemplemann and Womack, 1942, discuss the patho-genesis of mixed tumors and conclude that the staining reaction differs in mucoprotein in the stromal and parenchymal elements. The mesenchymal mucoids are more resistant to hot dilute sulfuric acid. The mucoid in myxomatous and cartilaginous areas behaves exactly as does the chondroitin sulfuric acid complex in skeletal cartilage, chondromata, chondrosarcomata, and walls of arteries showing mucoid degeneration. The mucoid within the acini stains as does the mucoprotein complex in mucin of the salivary gland, gastrointestinal and respiratory tract, and mucoid carcinoma of the intestine. Therefore, they conclude that there are two types of tissue in mixed tumors with the one type having an "organizer" affect on the other. They suggest that mixed tumors may be the result of a primary epithelial maldevelopment with mesodermal differentiation secondary to this epithelial disturb-ance. They cite as an example of this phenomena the tissue culture of breast epithelium which grows in

sheets unless some fibrous tissue cells are present when the epithelium is differentiated to form ducts.

Gaylor and Smith, 1936, state that mixed tumors originate apparently from epithelium and show true metaplasia, although there is possibility of stimulation of young cells by cancer cells. These tumors show more pleomorphic forms than any other kind except teratomas of the testicle.

The presence of two types of tissue in a tumor may be influenced by an inflamatory reaction in the tissue due to the tumor. Pearlman, 1940, states that chronic productive inflamatory changes may give rise to a cellular, dense stroma which may contain lympho-cytes and giant cells. Such a phenomenum might be responsible for some of the confusion met with in studies of mixed tumors.

Frank and Lev, 1940, discuss carcinosarcoma of the larynx and state that the specimens studied were carcinomas which had undergone morphological variation and the factors responsible for the sarcoma-like arrangement of cells were (1) inherent tendency of the tumor itself (2) amount of connective tissue environment of the tumor.

Workers who suggest a branchial arch derivation for mixed tumors are really endorsing the embryological derivation with just a more specific site of the cell rests. Forman and Warren, 1918, state that it seems probable that there is in the head and branchial region of the human embryo, mesenchyme which has been derived from ectoderm, and that inclusion or misplacement of this ectodermal mesenchyme gives rise to the so-called mixed tumors of the salivary glands. Assuming this hypothesis is tenable, it gives a ready explanation of the morphological behavior of the tumor cells. If these tumors arise from an inclusion or misplacement of mesenchyme derived from ectoderm, all tissues found can be accounted for at once. Either the cells fail to differentiate and simulate cells from which they arose, or they differentiate along the lines they normally do and form connective tissue, cartilage and, sometimes, bone.

CONCLUSIONS

1. Some of the great amount of literature on "mixed tumors" has been reviewed more for the purpose of showing the varied structure and unpredictable course of these tumors rather than to classify or explain their origin.

2. Mixed tumors are aptly named since they contain such tissues as squamous, columnar, cuboidal, glandular and ductal epithelium; hyaline, myxomatous and dense fibrous connective tissue; fat, cartilage and bone. These tissues have no constant relation to each other, and there is usually no definite line of demarcation between the types of tissue. Any tissue may be absent or present in varying quantities and serves very little for purpose of classification.

3. The course of mixed tumors is unpredictable. They do, however, tend to be of long duration and of benign character giving signs of their presence several years before medical advice is sought. Constant or rapid increase in size with local pressure symptons is the incentive which brings the patient to the doctor. Occurance of mixed tumors has no correlation with sex although the usual age period is from twenty to fifty years.

4. Prognostication on mixed tumors is very uncertain. Simple enucleation may give a permanent cure, or

result in recurrence months or years later. At present removal en bloc seems to be the safest procedure and gives the largest number of cures. Irradiation with or without surgery has been encouraged and condemned by various workers.

5. Several theories have been exponded on the origin of mixed tumors. The two most popular theories are those embracing the embryonal or the epithelial origin. The embryonal theory answers the question of mixed tissues adequately, but it is unsatisfactory in that it does not give any aid in classification of these tumors. The epithelial theory contends that cartilage is derived from the epithelium or is not really cartilage but an epithelial degeneration product and the tumor is not truly "mixed". Both theories have good points and the author does not feel qualified to make a choice.

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