AN INQUIRY INTO THE ORIGIN OF THE MIXED TUMORS OF THE SALIVARY GLANDS, WITH REFERENCE TO THEIR EMBRYONIC INTERRELATIONSHIPS

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There occurs in the salivary glands (1–5), buccal mucosa (6, 7), palate (8–11), cheeks and lips (12–15), antrum of Highmore (16–18), nares (19, 20), ethmoid sinuses (21), lacrimal glands (22), face (23–26), and elsewhere (27–41), a group of tumors about the origin of which an active controversy is still being maintained. These neoplasms are of composite structure, usually presenting epithelial elements in the form of cell strands, cell masses, alveolar arrangements, cartilage and pseudo-cartilage, myxomatous stroma, and cellular connective tissue. They have been grouped together as mixed tumors of the salivary glands. Those arising from other locations than the salivary glands are less complex in structure, and many of them fall into the group of cystic adenoid epithelioma (42, 43).

Regarding the origin of mixed tumors of the salivary glands, Ewing has summarized the present status of our knowledge as follows:

1. The endothelial origin has been disproved.
2. No single source of the mixed tumors meets all the requirements. Some are distinctly adenomatous and probably arise from acini and ducts of the gland in which they are well incorporated. Others are encapsulated or extraglandular, and take the form of basal-cell or adenoid cystic epithelioma. These probably arise from misplaced and occasionally embryonic portions of gland tissue. Branchial remnants may possibly be connected with this group.
3. The derivation of mucous tissue and cartilage from gland epithelium has been satisfactorily proved, and there is no necessity of including in the originating tissue any cartilaginous structures.''

Although there are numerous theories as to the nature and origin of these tumors, none of them seems to be adequate, nor do they throw any light on the question as to why most of these neoplasms are situated in the region of the head or why some extra-salivary gland tumors are of the cystic adenoid epithelioma type. The purpose of this communication is to describe some general features of these neoplastic growths, and to arrive at a probable explanation for their origin.

MATERIAL AND FINDINGS

The present study is based on 25 mixed tumors occurring in various locations in the head other than the salivary glands: 18 were located on the face and scalp, and 7 within the oral cavity. These tumors are interesting not only because of their unusual locations, but also be-
cause of certain histological features, the recognition of which should be helpful in understanding their origin and that of other, closely allied growths.

All these specimens were removed from Chinese patients. They are for the most part small, benign, well encapsulated tumors situated either in the skin or in the subcutaneous or submucosal tissues. It has not been considered necessary to include a detailed histological description of each of them. The findings are summarized in Table I. From this table, it is clear that these tumors occur inside as well as outside of the oral cavity. In the extra-oral tumors, the epithelial cells are in many instances of the basal-cell type (Figs. 1, 2, 3, 4). Cystic structures lined by stratified epithelium with cornification and rudimentary epithelial pearls (Figs. 1, 5, 6) are frequently encountered in this group (13 out of 18 cases), but in the intra-oral tumors epithelial pearls are only occasionally observed (1 in 7). Tubulo-alveolar structures (Fig. 2) and pseudo-cartilage are found only in the extra-oral tumors. The intra-oral tumors more often present the picture of cylindroma with peculiar cells having eccentric nuclei and acidophilic cytoplasm, conforming to Heineke’s description of Hyalinbildung (2).

**Table I: Findings in Cases Studied**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age in years</th>
<th>Sex</th>
<th>Location of tumors</th>
<th>Duration in years</th>
<th>Diameter in cm</th>
<th>Glandular structure</th>
<th>Tubulo-glandular structure</th>
<th>Epithelial pearls</th>
<th>Collagenized glands with cornification</th>
<th>Sebaceous cells</th>
<th>HyaZifibildung</th>
<th>Mucous</th>
<th>Hyaline</th>
<th>Pseudo-cartilage</th>
<th>Calcification</th>
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<td></td>
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<td>2</td>
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<td>2</td>
<td>30 m</td>
<td></td>
<td>Left eye brow</td>
<td>10</td>
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<td>3</td>
<td>35 m</td>
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<td>Left upper eye lid</td>
<td>3</td>
<td>11</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
<td>30 m</td>
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<td>Left side of nose</td>
<td>4</td>
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<td>20 f</td>
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<td>8</td>
<td>50 m</td>
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<td>Region of left nostril</td>
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<td>3</td>
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<td>9</td>
<td>73 m</td>
<td></td>
<td>Upper lip (in the skin)</td>
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<td>3</td>
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<td>10</td>
<td>33 f</td>
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<td>Upper lip (in the skin)</td>
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<td>11</td>
<td>27 m</td>
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<td>Upper lip (in the skin)</td>
<td>2</td>
<td>3</td>
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<td>12</td>
<td>32 f</td>
<td></td>
<td>Upper lip (under mucosa)</td>
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<td>1</td>
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<td>13</td>
<td>43 m</td>
<td></td>
<td>Chin</td>
<td>3</td>
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<td>14</td>
<td>22 m</td>
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<td>Chin</td>
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<td>15</td>
<td>25 m</td>
<td></td>
<td>Left ear</td>
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<td>2</td>
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<td>16</td>
<td>17 m</td>
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<td>In front of right ear</td>
<td>4</td>
<td>3</td>
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<td>17</td>
<td>30 m</td>
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<td>Pinnas of left ear</td>
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<td>18</td>
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<td>Hard palate</td>
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allied to them, e.g., the branchial dermoids, adamantinoma, basal-cell epithelioma, and cystic adenoid epithelioma.

**Histological Considerations**

1. *Extra-oral Tumors, Intra-oral Tumors, and Mixed Tumors of the Parotid Gland*: All these tumors have been grouped together because of their structural similarities (1, 2, 4, 9, 33). The present study shows a much higher frequency of squamous epithelium, cornification and pearl formation in the extra-oral tumors than in the intra-oral and salivary gland growths (9). The extra-oral neoplasms are less complex than the parotid tumors.

![Figure 1](image-url)

**FIG. 1. CASE 5: LOW-POWER VIEW (X 156) SHOWING SQUAMOUS EPITHELIUM-LINED CYST CONTAINING LAMINATED KERATIN LYING IN A MYXOMATOUS STROMA**

A few pseudocartilaginous cells are seen in the stroma. Islands of basal-cell epithelium with superficial palisade layer are shown at the left side of the picture.

2. *Mixed Tumors of the Parotid Gland and Branchial Tumors*: Complex teratoid tumors of the neck are comparatively rare, being found chiefly in connection with the branchial clefts and thyroid. They usually contain very complex structures, e.g., bone, teeth, muscle, ectodermal and endodermal cysts, and sometimes brain tissue (43). Chevassu (44) has shown that branchial cysts may contain pharyngeal epithelium and salivary gland tissues, the presence of which furnishes satisfactory evidence for the origin of some of the salivary tumors in this location. There are also tumors of a less composite structure occurring in the various fissures of the head and neck, and presenting features of mixed tumors of the parotid.

3. *Mixed Tumors and Adamantinoma*: In adamantinoma three structural types may be recognized: (1) acanthoma, (2) plexiform epithelioma, (3) glandular adamantinoma (45). The resemblance of the
mixed salivary gland tumors to adamantinoma has been mentioned by Kaufmann and Lang (4, 46).

4. **Mixed Tumors and Basal-cell Epithelioma**: Krompecher (25, 26) emphasizes the close relationship between mixed tumors and basal-cell epithelioma. He even suggests calling the former mucoidaline basal-cell epithelioma. Anitschkow (35) interprets his case of epithelioma of the scalp, which is very similar to Case 1 of this series (Figs. 7, 8),
as a transitional form between the mixed and basal-cell epithelial tumors. The mixed tumors usually have more complicated structures than the basal-cell epitheliomas, in which only masses or strands of basal epithelium are seen.

5. **Extra-oral Mixed Tumors and Cystic Adenoid Epithelioma:** It has already been mentioned that extra-oral tumors resemble other mixed tumors in the multiplicity of their component elements, while differing
from them more or less in the presence of epithelium of the basal type and in the frequent occurrence of squamous epithelium with a tendency to cystic formation and cornification—an observation which indicates a close relationship between extra-oral tumors and cystic adenoid epithelioma.

Cystic adenoid epithelioma, according to Gans (47), is characterized by a close connection with the skin without encapsulation and the constant presence of cystic structures lined by squamous epithelium with cornification, of hair follicles, sometimes of lanugo hairs, of sebaceous glands, and of myxomatous stroma, cartilage, and bone.

Vörner's case of mixed tumor of the skin of the ala nasi (37) showed the presence of a complete capsule, with bone, cartilage, myxomatous stroma, epithelial cell strands, cystic and glandular structures, squamous epithelial cystic formation, cornification, lanugo hairs, hair follicles, and sebaceous glands. Gerlach (32) stated that his case of mixed tumor of the eyebrow closely resembled cystic adenoid epithelioma, except for the presence of cartilage and myxomatous stroma. Sebaceous cells were found in two of the present series (Fig. 9, Cases 9, 11). These instances may be interpreted as transitional forms between extra-oral tumors and cystic adenoid epithelioma.

Histogenetic Considerations

Histogenesis of Mixed Tumors; Ectodermal or Combined Ectomesodermal Origin: The occurrence of squamous epithelium in extra-oral tumors has been repeatedly described (22, 25, 26, 36, 32, 38, 13, 24). It has also been recorded in mixed tumors of the salivary glands and of the palate (48, 1, 49, 25, 26, 9), and has been considered by various workers to indicate an epithelial origin of these tumors.
With reference to the presence of cartilage in the tumors, Marchand
(50) believes that it probably originates from the epithelium, and the
name pseudo-cartilage is therefore suggested. In these areas the ep-thelial cell strands separate into single cells which become enclosed in
a homogenous mucinous ground substance. Ehrich (49) considers the
myxomatous stroma and cartilaginous tissue as secretion products of
the epithelial parenchymatous tissue. Forman and Warren (51) are
of the opinion that the ectoderm has the potentiality to form cartilage
and that mixed tumors can possibly be explained on the basis of a
purely epithelial origin. Kaufmann (46), after studying 50 cases,
also favored an epithelial origin. According to him the extremely
variable pictures in basal-cell carcinomas, and in the enamel organs
and their tumors, indicate the possible variability of ectodermal cell
proliferation, especially in the case of transition forms of ectodermal
into apparently mesenchymal structures. Wilms, however, believes
that the tumors are derived from scattered germinal tissue of the oral
invagination, epithelial and connective tissue. Böttner (52) assigns
an unimportant rôle to the mesodermal element in their origin. He
does not favor the term mixed tumor, since the lesions are in reality
uniform benign epithelial neoplasms.

Most investigators agree that mixed tumors are of epithelial origin
or of combined ectodermal and mesenchymal origin, in which the ep-thelial element plays the more important rôle. There exists at present
little difference of opinion about the origin of the mixed tumors in
embryonic tissue displacements or embryonic rests, and most workers
do not question that there is a congenital anlage behind these tumors
(1, 4, 53). There is, however, much disagreement as to the time and

\textbf{Fig. 7. Case 1: Low-power View Showing Epithelial Cells of Basal-cell Type with
Formation of Glandular Structures and an Abundant Amount of Mucin in the Stroma}
site of such displacement (2). Some assume that the rests result from disturbances in the development of branchial arches (2) and various complicated fissures of the face (54). Still others think they result from developmental disturbances of the salivary glands (55, 56). Hinsberg, for example, states that the embryonic rests are formed at a time when the branchial arches have already disappeared (in the 8th and 9th week of embryonic life), and are composed of lobes of salivary gland and some periosteal or perichondrial tissue caught along with them (55). Wilms, on the other hand, thinks that the rests are formed at a much earlier period and that both the salivary gland and the embryonic rests come from the oral ectoderm, which at that time still possesses the ability to form oral mucosa and glandular tissues.

![Image](image_url)

**Fig. 8. Case 1: Low-power View (X 156) Showing Epithelial Cell Strands Dispersed in Mucinous Stroma**

2. **Histogenesis of Allied Tumors of the Salivary Glands:** Branchial teratoids or dermoids have been traced to congenital anomalies arising from irregularities in the closure of the branchial clefts resulting in ectodermal inclusions (43). In a similar manner adamantinoma has been traced to the anlage of the enamel organ, and cystic adenoid epithelioma to faulty anlagen of hair follicles (43, 47). The basal-cell epithelioma has been recently traced to hair follicle epithelium (58).

If one accepts Wilms’ interpretation, the origin of intra-oral tumors and salivary gland tumors is readily explained. As the extra-oral tumors show no apparent relationship in their location to the salivary glands and do not appear in close approximation with the various fissures of the face and neck, their origin from oral ectoderm or from faulty closure of various fissures of the face and neck is unlikely. Some other explanation seems necessary to account for their occurrence. Since they show resemblances to the cystic adenoid epithelioma, which
is considered by many authors as being derived from embryonic rests of hair follicles, the simplest explanation is to assume an embryonic relationship of the anlagen from which the two tumor types arise.

Concerning embryonic anlagen or rests, commonly attributed to some developmental disturbance, there are three factors to be considered: (1) the process and manner in which the rests are formed, (2) the embryonic period in which they arise, and (3) what stimulates the rests to growth. The first question has been well summarized by Albrecht (59). The third still remains a mystery. It is the purpose of this paper to emphasize the importance of the time factor in relation to the potentiality of the tumor anlagen.

With regard to such a time factor, Borst (60) says: “The earlier

![Figure 9](https://via.placeholder.com/150)

FIG. 9. CASE 11: HIGH-POWER VIEW (× 300) SHOWING A MASS OF SQUAMOUS EPITHELIUM CONTAINING SEBACEOUS CELLS AND PART OF A CYST LINED BY SQUAMOUS EPITHELIUM

such a germ is separated during embryonic development, the greater will be its developmental possibilities or prospective potentialities and the more manifold the tissue it produces in tumor-like growth.”

Mixed tumors are regarded by MacCallum (61) as teratomata derived from the isolation of cells in an advanced state of differentiation, whose capabilities are therefore limited and fairly strictly determined. Eggers (9) is of the opinion that the initiation of displacement of embryonic rests could probably occur at different periods of development and specialization, and this would account for the varied morphology of the mixed tumors.

Tissue specialization and potentiality are governed by the law of genetic restriction (62). By this law we understand that as development advances a constantly increasing restriction is imposed on the various tissues as to their differentiation. Each emerging tissue is
more rapidly bound to its particular type of differentiation than the less specialized parent tissue. A line of specialization once begun cannot revert to another type. The parent tissue, likewise, is limited by losing its capacity for duplicating anlagen already formed.

In the formation of different tissue anlagen, the ectoderm is subjected to a series of folding, fusion, and invagination. It is highly possible and conceivable that tumor rests are formed along with normal tissue anlagen. The neural groove appears and closes between the third and fourth week. Branchial clefts appear and close between the latter part of the fourth and the end of the sixth week. Salivary glands, nasal and lacrimal glands are formed between the early part of the sixth and the end of the ninth week. Enamel organs are formed in the sixth week. Hair follicles appear first in the eyebrow, lips, and chin in the eighth week and later elsewhere in the face. They appear over the general body surface by the thirteenth week. Anlagen of sebaceous and sweat glands are formed later (63, 64, 65). It is clear that the ectoderm forms nervous and glandular (both mucous and serous) tissue, hair follicles, sebaceous and sweat glands in successive periods, and the parent tissue gradually loses its potentiality for duplicating the same. It is logical to believe that the embryonic rests formed at earlier periods have greater potentiality than those formed at a later period. What is more important than the process or manner in which the rests are formed is the influence of the time factor on their potentiality and the composition of tumors.

It is highly probable that at the end of the fifth week, when the anlagen of the nervous tissue are already completed and the anlagen of the glandular tissue first appear, the parent tissue loses its capacity for forming nervous tissue. At the end of the ninth week when the anlagen of the various glands are completed, the parent tissue loses the potentiality for forming glandular tissue. On the basis of the above conception, a purely theoretical scheme, represented by Table II has been worked out. In this diagram the periods of formation of normal tissue anlagen and their possible tumor rests are represented by heavy vertical lines, and the expected characteristics of tumors arising from various rests are indicated. The embryonic rests formed before the sixth week will give rise to teratoid or dermoid growths, as the rests at that time retain all the potentialities of the ectoderm. The rests formed in the sixth to tenth week, having no potentialities to form nervous tissue, will give rise to tumors of a less composite structure, comprising all the tumors of the mixed series. The rests formed from the tenth week on, before the potentiality for forming hair follicles is lost, will show a tendency to produce the so-called cystic adenoid epithelioma.

On the supposition that the embryonic rests are formed in association with normal tissue anlagen, these tumors would be expected only in certain locations. Thus, the branchial tumors are found in the course of the various fissures of the head and neck; adamantinomas in the jaws; mixed tumors in the head and face and not below the neck; cystic adenoid epithelioma on the head, face, and general body surface.
This agrees fairly well with clinical observations on the frequency and location of these tumors. Though it is very unlikely that tumor anlagen are formed independently of the normal tissue anlagen, yet, should this happen through some embryonic disturbances, the resulting tumor would still be determined by the time when its anlage was formed. Thus, adamantinomas and mixed tumors under very unusual conditions, would occur in places other than the usual locations (66, 27, 34).

Table II: Origin of Mixed Tumors in Relation to Periods of Embryonic Rest Formation

<table>
<thead>
<tr>
<th>Week of embryonic life</th>
<th>Periods of formation of normal tissue anlagen and associated embryonic rests</th>
<th>Expected nature of the tumor</th>
<th>Expected location of the tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th</td>
<td>Fusion of branchial cleft; embryonic rests</td>
<td>Teratoid</td>
<td>Region of branchial cleft</td>
</tr>
<tr>
<td>6th</td>
<td>Fusion of branchial cleft; embryonic rests</td>
<td>Mixed tumor, adamantinoma</td>
<td>Region of branchial cleft</td>
</tr>
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<td></td>
<td>Anlage of enamel organ (dental ridge); embryonic rests</td>
<td>Mixed tumor</td>
<td>In the jaw, parotid region</td>
</tr>
<tr>
<td></td>
<td>Anlage of parotid; embryonic rests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7th</td>
<td>Anlage of submaxillary gland; embryonic rests</td>
<td>Mixed tumor</td>
<td>Submaxillary region</td>
</tr>
<tr>
<td>8th</td>
<td>Anlage of sublingual gland; embryonic rests</td>
<td>Mixed tumor</td>
<td>Sublingual region</td>
</tr>
<tr>
<td></td>
<td>Anlage of alveololingual gland; embryonic rests</td>
<td>Mixed tumor</td>
<td>Within the oral cavity, face and scalp</td>
</tr>
<tr>
<td></td>
<td>Anlage of hair follicles of eyebrow, lips, chin, face, etc.; embryonic rests</td>
<td>Mixed tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anlage of glands in nasal cavity and its sinuses; embryonic rests</td>
<td>Mixed tumor, cystic adamantoid epithelioma</td>
<td>Nasal cavity and its sinuses, orbital region</td>
</tr>
<tr>
<td>9th</td>
<td>Anlage of hair follicles of face; embryonic rests</td>
<td>Cystic adamantoid epithelioma</td>
<td>Face and scalp</td>
</tr>
<tr>
<td>10th</td>
<td>Anlage of hair follicles of the general body surface; embryonic rests</td>
<td></td>
<td>General body surface</td>
</tr>
</tbody>
</table>

The expected frequency of these tumors corresponds with the length of the period of their rest formation. This again is in agreement with clinical experience.

Table II shows, in addition, that the embryonic rests from which the mixed tumors are derived have several sources of origin and are formed at different embryonic periods along with the normal tissue anlagen. Some rests are formed from ectodermal inclusions in the fusion of branchial clefts in the sixth week, after the ectoderm has lost its potency for nervous tissue formation. These will be responsible for tumors found in the vicinity of the branchial fissures. Since these rests are formed in a similar manner and from the same sources as other branchial inclusions, except at a later period, when the anlage for the parotid is formed, the resulting tumor will show characteristics of mixed tumor of the parotid, and bear a closer relationship to other branchial teratoids. Some rests are formed from the oral ectoderm along with the anlagen of the parotid, submaxillary, sublingual, molar
and alveolo-lingual glands from the sixth to the end of the ninth week. These will give rise to mixed tumors in the salivary glands and other tumors within the oral cavity. As the embryonic rests are formed at such varying periods of time, it is natural to expect that the tumors arising from them will show a wide variation in their minute structures aside from their group characteristics. Some rests are formed in the nasal cavity and its air sinuses along with the normal glandular anlagen in the ninth week. They will be responsible for the mixed tumors in these regions. Some rests are formed in the conjunctiva along with the anlagen of the lacrimal glands, in the ninth week. They will give rise to the mixed tumors of the orbital region. Other rests are formed from the integument along with the hair follicle anlagen in the eighth and ninth weeks. Such rests will give rise to the mixed tumors of the face and scalp. Others formed later, after the ectoderm has lost its potentiality for glandular tissue formation, will give origin to cystic adenoid epithelioma. The resulting tumor, therefore, will show both the characteristics of mixed tumors and, at the same time, resemblance to cystic adenoid epithelioma.

**Summary**

(1) Mixed tumors are probably embryonic tumors of local origin. From histological, regional, and histogenetic points of view, they seem naturally to fall into two groups, intra-oral and extra-oral. To the first group belong tumors arising from oral ectoderm, lying within the oral cavity, including tumors of the palate, gum, tongue, salivary glands, etc. The embryonic rests from which these are derived are formed along with the salivary and oral glands, from invagination of the oral ectoderm as assumed by Wilms. To the second group belong tumors of extra-oral origin: (a) tumors resulting from ectodermal inclusions caused by the fusion of branchial clefts and various fissures of the head and neck; (b) tumors of the nasal cavity and its accessory sinuses arising from rests formed along with the normal mucous glands of these regions; (c) tumors of the orbit derived from rests formed from the conjunctiva together with the anlagen of the lacrimal glands, (d) various other mixed tumors of the lip, face, eyebrow, scalp, etc., assumed to have arisen from rests derived from the integument along with the anlagen of the hair follicles.

(2) The histological similarities and differences among the mixed tumors and tumors closely allied to them are explained by differences in the origin and time of their rest formation. The location and frequency of occurrence are explained on the same ground.

(3) The influence of the time factor in the formation of embryonic rests upon their expected potentiality is specially emphasized.

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