# HISTOGENESIS OF PAPILLARY CYSTADENOMA LYMPHOMATOSUM (WARTHIN'S TUMOR) OF THE PAROTID SALIVARY GLAND *

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For many years prior to 1910 authors sought to include the neoplasm known today as papillary cystadenoma lymphomatosum among the tumors of the lateral cervical cysts. In that year papillary cystadenoma lymphomatosum was recognized as a distinct entity for the first time (Albrecht and Arzt[1]), and final separation was attained from branchiogenic and dermoid cysts. Following this publication many names for the neoplasm were proposed, but with the well known paper by Warthin[2] in 1929, the designation of the tumor as papillary cystadenoma lymphomatosum was generally accepted.

The contribution of Albrecht and Arzt[1] should have crystallized the definition of this neoplasm, and to some extent clarified its histogenesis. Such has not been the case. It is believed that the greater part of the subsequent confusion has stemmed from: (1) the designation of any tumor in the cervical region with a cystic and papilliferous pattern as papillary cystadenoma, (2) the indiscriminate inclusion under the term adenolymphoma of the Warthin tumor along with other tumors (used in a broad sense) that occur in the parotid gland region[3-7] and consist of lymphoid and epithelial elements, and (3) the designation of the papillary cystadenoma lymphomatosum by many names derived from various concepts of its histogenesis (Table I). Because of this confusion, it has not been possible to collect all of the typical cases from the literature with accuracy.

In our survey, 163 acceptable cases have been found.[1-12,14-19,21-68] Some of these cases[8,18] have been included with hesitancy. This is true also of 2 of Lederman's cases (a 66-year-old male and a 42-year-old female).[56] There have been others for which the original articles have not been available; these have been included because those citing them gave evidence of being familiar with the neoplasm under consideration. Thus we have included cases by Ruiz,[69] cited by Niño[50]; Mosto[70] and Marvel,[71] cited by Duany[14] and Niño[50]; Bianchi and Pavlovsky[72] and Matsushima,[73] cited by Duany[14]; Putschar[74] and Wohlwill,[75] cited by Berner[55]; and Ehrlicher,[13] cited by Duany.[14] Some reported cases have been excluded,[76-79] primarily because the data recorded have not been considered adequate. Berner's[55] case 5 and Nicholson's[15] case 1 have been excluded for this reason. Some cases have been reported by differ-

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ent authors; these include cases by Plaut[7] and Martin and Ehrlich,[26] and by Harris[25] and Swinton and Warren.[30] Whenever duplication has been recognized these cases have been included only under the original report.

Of the 180 acceptable cases (163 from the literature and 17 reported here for the first time) of papillary cystadenoma lymphomatosum, all

TABLE I

*Names Applied to the Papillary Cystadenoma Lymphomatosum by Various Authors*

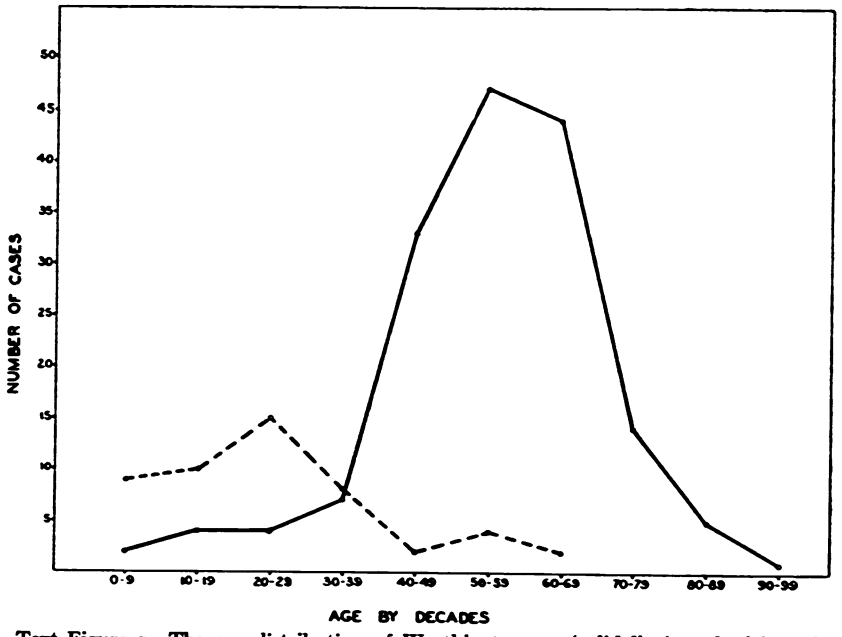
| Authors | Diagnoses |
|---|---|
| Hildebrand[8] | Congenital epithelial cyst of the neck |
| Lecène[9] | Cystic adenoma of the parotid gland |
| Albrecht and Arzt[1] | Papillary cystadenoma in typical lymph node |
| Glass[10] | Branchiogenic papillary cystadenolymphoma |
| Ssobolew[11] | Branchioma |
| Feldmann[12] | Branchiogenic adenoma |
| Ehrlicher,[13] cited by Duany[14] | Papillary cystadenoma with lymphoid supporting tissue |
| Nicholson[15] | Cystic papillary adenoma |
| Mazza and Cassinelli[16] | Papillary cystadenolymphoma |
| Menetrier, Peyron, and Surmont[17] | Kyste amygdaloïde |
| Hickel[18] | Tumeur amygdaloïde polykystiques |
| Stöhr and Risak[19] | Cystadenolymphoma parotidis |
| Askanazy,[20] cited by Sternberg[21] | Adenoma branchiogenes cylindrocellulare cysticum |
| Warthin[2] | Papillary cystadenoma lymphomatosum |
| Bottin[22] | Papillary cystadenoma |
| Jaffé[23] | Onkocytoma |
| Kraissl and Stout[24] | Cystadenoma (orbital inclusion cyst) |
| Hall[3] | Adenolymphoma (orbital inclusion adenoma) |
| Harris[25] | Adenocystoma lymphomatosum |
| Martin and Ehrlich[26] | Warthin's tumor |

were located in the region of the parotid gland except 5. One was from the submaxillary gland region,[32] and 4 were supposedly from the submaxillary salivary gland itself.[1,32,34,38] In 10 patients, the condition was bilateral. The sex was indicated for 141 males and 19 females, a ratio of roughly 7 to 1. The age distribution is shown in Text-Figure 1.

If the Warthin tumor is to be included in the general group of benign lympho-epithelial tumors designated as adenolymphoma, this should be done with discrimination. That all of the tumors included under this term are true neoplasms is far from certain. In the parotid salivary gland area, lymph nodes containing included salivary gland ducts (as will be described subsequently) may be the seat of chronic hyperplastic lymphadenitis secondary to some inflammatory process about the head or neck. Some of these may have been considered erroneously as true adenolymphomas. However, the tumor of Albrecht and Arzt,[1] which at the present time is designated as papillary cystadenoma lymphomatosum, is accepted as a true neoplasm. An additional factor that must be taken into consideration is the more aggressive character of some

true adenolymphomas (not Warthin tumors) which has led to the opinion that they may be carcinomatous.[62] A tumor of this character (3654–AX) has been seen in this laboratory.

No convincing examples of carcinomatous change in a Warthin tumor have been encountered in the literature or seen in our material. In Ssobolew's[11] case, carcinoma could be demonstrated in only one of




Text-Figure 1. The age distribution of Warthin tumors (solid line) and of branchial cysts and fistulas (broken line).

three pieces of tissue available for study. He could not establish a relationship between the carcinoma and the papilliferous cystadenoma lymphomatosum present in the remainder of his material. The author's photomicrograph of the carcinoma is not sufficiently clear to be evaluated. The clinical course could not be followed because of the early death of the patient from another cause. This case may be similar to case 7 of our series in which a Warthin tumor and a carcinoma were found in material removed from the left parotid region. However, no relationship could be demonstrated between the two. Hanford's[36] second case may be in this category also, as the evidence of carcinoma arising in the initial neoplasm cannot be considered proved. We cannot accept a diagnosis of carcinoma on the evidence submitted by Stöhr and Risak,[19] although this case has been so considered by some authors.[55,64] Gödel[46] and Lederman[56] have not established convincingly the presence of a Warthin tumor in their cases.

An evaluation of the characteristics of other adenolymphomas produces some interesting data, when contrasted with the features of the Warthin tumor. Twelve such cases have been gathered from the literature.[7,62,81,82] One has been considered as showing sarcomatous change in the supporting lymphoid stroma,[82] and one has been interpreted as carcinoma.[62] Seven of the 12 are reported as occurring in females, 4 in males, and the sex is not indicated in one. While no definite conclusions can be derived from the review of only 12 cases, these data are presented for what they may be worth as indicating dissimilarity when compared with true papillary cystadenoma lymphomatosum.

It is considered that the foregoing observations make it imperative to maintain the Warthin tumor as a distinct entity in the group of adenolymphomas that are true neoplasms.

It is our purpose to re-define the papilliferous cystadenoma lymphomatosum, and to evaluate the various concepts concerning its histogenesis. Particular attention has been given certain disputed histologic features of the neoplasm: the presence of ciliated epithelium, the presence of secretory capillaries, the presence of squamous epithelium, and whether the lymphoid elements represent true lymphnodal tissue.

## Materials and Methods

The material utilized in this study has been arranged in four groups: human embryos, presumably normal parotid and submaxillary salivary glands, accepted branchiogenic residual structures, and neoplasms having the features of Warthin's tumor.

Through the courtesy of the Department of Anatomy of the University of Michigan Medical School, it was possible to examine serial sections of the head and neck of 18 embryos, varying in crown-rump length from 20 to 200 mm. This material constituted group 1. Attention was directed to the development of the parotid, submaxillary, and sublingual salivary glands.

The materials selected for the second group were divided into two parts. Part 1 consisted of 100 normal parotid salivary glands obtained at necropsy from patients dying of causes unrelated to the face, mouth, and neck. The ages at the time of death varied from the seventh month of gestation to 75 years. Thirty-five glands were from females, and 65 were from males. Approximately two-thirds of each gland was removed for study, and from each gland two blocks, on the average, were prepared. Eighty of the glands were fixed in formalin and 20 were fixed in absolute alcohol. The sections were stained with hemalum and eosin. This material has served as a basis for two previous studies.[83,84] Part 2

of this group was composed of 50 submaxillary salivary glands. Two of these were removed during post-mortem examination, and 2 presenting the features of chronic sialadenitis were removed surgically for that condition. The remaining 46 glands were included in the material from suprahyoid cervical lymph node dissection in patients with carcinoma of the face, lips, or mouth. All patients were adults and a majority were in the fifth and sixth decades. One or two blocks of tissue were available for study in each instance. All tissues were fixed in formalin and stained with hemalum and eosin.

Fifty branchiogenic cysts and fistulae were selected at random to constitute group 3 of this series. The variation in age of these patients was from 4 to 40 years (Text-Fig. 1). The cases were about equally distributed between the sexes. In the majority only one microscopic section was examined.

TABLE II

*Twenty-three Examples of Papillary Cystadenoma Lymphomatosum Comprising Group 4 of the Material Studied*

| University of Michigan series | | | | |
|---|---|---|---|---|
| Number | Identification of case | Age | Sex | Location |
| 1 | 6630–AL | 45 | M | Right |
| 2 | 5759–AN | 68 | M | Right |
| 3 | 122–AR | 65 | M | Left |
| 4* | 1285–AS | 63 | M | Left |
| 5 | 3989–AU | 60 | M | Left |
| 6 | 5337–AV | 70 | M | Left |
| 7 | 49–AW | 61 | F | Left |
| 8 | 3807–AX | 50 | M | Right |
| 9* | 1542–AY | 65 | M | Left |
| 10† | 1431–LAD | 45 | M | |
| 11† | 4887–LAF | 60 | M | Left |
| 12‡ | 3358–LAH | | | |
| 13§ | 3306–LAK | 50 | M | Right |
| 14 | 4230–LAQ | 60 | | |
| 15 | 7681–LAV | 51 | M | |
| 16 | 9217–LAX | 64 | M | |
| 17 | 1789–LAY | 62 | M | |
| 18 | 4152–LAY | 70 | M | Right |
| 19 | 6053–LAZ | | | |
| 20 | 2450–LBA | 45 | M | |
| 21 | 7653–LBA | | M | |
| 22‖ | 44–1193 | 50 | M | Right |
| 23‖ | 45–1964 | 55 | M | |

* Reported by Kerr.[68]
† Reported by Warthin.[2]
‡ Reported by Wendel.[84]
§ Reported by Odén.[41]
‖ From St. Joseph's Mercy Hospital.

Twenty-three examples of papilliferous cystadenoma lymphomatosum comprised the fourth group (Table II). Twenty-one cases were from the Department of Pathology of the University of Michigan. Nine of these were from the University Hospital and 12 cases from the extra-

mural diagnostic service. Two cases were from the laboratory of pathology, St. Joseph's Mercy Hospital. Six of the 23 have been reported previously. Cases 10 and 11 were the basis of Warthin's report [2] in 1929. Case 12 was described by Wendel [34] in 1930. This was the only instance in this series of papillary cystadenoma lymphomatosum supposedly arising in the submaxillary salivary gland. Case 13 was reported by Odén [41] in 1935. Cases 4 and 9 were mentioned by Kerr [63] in 1947. The 11 cases from the University and St. Joseph's Mercy hospitals were from the parotid gland or its immediate vicinity. The cases from the outside diagnostic service were, so far as known, all from the same area. The original tissues in group 4 were fixed in formalin and stained with hemalum and eosin. From the material from the University Hospital, sections 5 $\mu$ in thickness were counter-fixed in slightly acidified Zenker's solution at room temperature for 6 to 8 hours, then stained by the Goldner [85] modification of the Masson trichrome technic. Mallory's aniline blue, orange G, and acid fuchsin technic was found to be unsuitable because nuclear detail was masked.

## Embryology

The embryology of the major salivary glands must be considered briefly, with only those features that contribute to the elucidation of the histogenesis of the Warthin tumor given detailed presentation. The reader may refer to standard texts on developmental anatomy [86-90] for additional information.

The anlagen of the parotid and submaxillary salivary glands appear in man during the sixth week of embryonic life.[87-90] The buccal sulcus gives rise to two derivatives: the orbital inclusion from a more posterior position [87,88,91] (Fig. 1), and the parotid anlage from a more anterior portion [87,88] (Fig. 2). The existence of the orbital inclusion in man has been denied.[62] The submaxillary salivary gland anlage, and, later, those of the sublingual glands, arise from the alveololingual sulcus.

Schulte [87] and Carmalt [88] described the orbital inclusion, once it has been separated from the oral epithelium, as being displaced laterally and coming to lie close to the muscles of mastication. It progresses caudally, medial to the masseter muscle (Fig. 3), to a position against the internal pterygoid muscle. The orbital inclusion is derived from a segment of the buccal sulcus, which subsequently gives rise to the orbital glands in some carnivora. The significance of the presence or absence of an orbito-parotid interval or an orbito-parotid area of the buccal sulcus between the parotid gland and orbital inclusion anlagen need not

be considered at this time. Occasionally separate glandular masses are found in relation to the intramural and buccinator portions of the parotid duct in man.[87,88] These do not communicate with the parotid duct, but open by small, independent, separate orifices on the oral mucosa posterior to the opening of the parotid duct. When well developed, a series of these glands may be imbedded in the fat pad medial to the masseter muscle. This series represents the reduced human representatives of the orbital glands in some carnivora.

The epithelial anlage of the parotid gland may be traced in a caudal direction from its point of origin. The epithelial cylinder traverses the external surface of the masseter muscle (Fig. 3), to the retromasseteric locus of the parotid gland. The duct ramifies freely into cell cords, which eventually differentiate into branching ducts and alveoli. Aggregates of "round cells" are noted in the parotid gland region in embryos of a crown-rump length of 20.5 mm. At this stage it is not possible to identify these elements as lymphocytes. Lymphoid tissue was identified in this area in an embryo with crown-breech length of 60 mm. and in other fetuses through the oldest specimen in this series which had a crown-rump length of 200 mm. In this material lymphoid tissue was observed to exist as lymphoid aggregates and lymph nodes in embryos of 89, 105, and 200 mm. crown-breech length (Figs. 4 and 5). It was particularly impressive to note the absence of lymphoid elements in the submaxillary and sublingual glands of the same embryos.

An additional significant embryologic observation has to do with the comparative dispatch with which the organoid integrity of the salivary glands is established. In embryos as young as 7½ weeks the submaxillary gland gave the impression of developing as a unit. From this stage through that of a 14-week embryo there was a tendency for the submaxillary salivary elements to appear as a compact organoid entity, developing as a unit within a capsule formed by the condensation of mesenchyme (Fig. 6). On the other hand, the parenchymal elements of the parotid gland were arranged in a loose manner, and had a "sprawled out" appearance (Fig. 7). No evidence of mesenchymal condensation to form a capsule was apparent in our specimens until the 105 mm. (14 weeks) stage. In some of the slightly older embryos (100, 105, 200 mm.) there were lymph nodes containing salivary gland ducts (Fig. 5) inside and outside of the capsular area of the parotid gland. The sublingual gland, as far as capsular development is concerned, also appeared to evolve in a more closely integrated manner than the parotid gland.

## The Control Series of Parotid and Submaxillary Salivary Glands

### *Parotid Gland*

In general, the results of our study of normal parotid salivary glands are in agreement with the descriptions in the standard textbooks of histology. One of the more significant findings in 25 of this group of 100 was the presence of lymphoid aggregates surrounded by fibrous connective tissue stroma within the gland proper. In approximately two-thirds of the 25 cases, some or all of the characteristic features of lymph nodes (differentiation into cortex and medulla, lymphatic sinuses beneath the capsule and in the medullary area) were apparent. The aggregates varied in volume within the usual range of lymph nodes. Whether some of these lymphoid aggregates should be designated as lymph nodes has been debated.[26,46] It is not pertinent to enter into the discussion here. Suffice it to say, that lymph nodes in other areas of the body may exhibit histologic features which are not in complete accord with the usual morphologic pattern. In unquestioned lymph nodes of the parotid gland, the lymphnodal features in many instances are not as distinct or as clearly defined as in lymph nodes from some other regions. This may be due in part to the increased development of fibrous connective tissue stroma in the lymph nodes of the parotid gland area. Henceforth, the larger encapsulated lymphoid aggregates will be referred to as lymph nodes.

In 6 of the 25 cases, parotid gland ducts were identified in lymph nodes (Figs. 8, 9, and 10). The ages of the patients were the 7th month of gestation and 22, 34, 37, 54, and 60 years. In some instances a lobule of the gland could be seen extending into the hilus of a lymph node (Fig. 11). This feature was noted also in a few of the remaining 19 cases. The fact that all of these 6 cases were in males was considered significant, since the ratio of males to females with lymph nodes in the parotid gland was reasonably close statistically to the sex ratio for the total 100 cases.

The epithelium lining the duct system of the parotid gland was found to correspond to the descriptions in the literature with few exceptions.[92] Ciliated epithelium could not be demonstrated in any of the ducts. In the glands of patients of more than 50 years of age, oxyphilic granular cells[83] (pyknocytes[93] or oncocytes[94]) were present as noted previously by Meza-Chávez.[83] Ducts showing transition of the epithelium from the usual type to the oxyphilic granular type were demonstrable (Figs. 12 and 13). In a few cases, ductal epithelial cells were seen that corresponded to a type previously described[92] as occurring in tumors of the

salivary glands (Fig. 14). These cells, designated "clear cells" in the past, should be considered in the majority of instances as ductal epithelial cells partially or wholly devoid of cytoplasmic granules. In one example (case 9), such cells formed the sole type of epithelium lining several excretory ducts. In this case, transitions from ductal epithelium of the oxyphilic granular type to the clear type could be demonstrated. Such a change was apparent also in the acinar cells. Since the integrity of the nuclei was maintained as a rule, these cytoplasmic changes were interpreted as being related to some unusual metabolic or secretory activity, rather than to retrogressive changes. Occasionally, as among the oxyphilic granular cells, clear cells could be seen with indented or pyknotic nuclei. With the exception of the character of the cytoplasm, these cells corresponded in physical appearance to the oxyphilic granular cells. This was interpreted as indicating that the clear cells of the ductal epithelium probably are derived from the oxyphilic granular cell variant of the usual ductal epithelium, and that the oxyphilic granular cell and the clear cell are both normal variants of the ductal epithelium, the oxyphilic granular cell being related to the ageing process, and the clear cell being a manifestation of hypersecretion or some other metabolic change.

At infrequent intervals ducts were seen lined by true goblet cells. These were distinctly different from the cells described in the preceding paragraph, and they appeared to be more closely related to the usual parotid ductal epithelium of younger individuals. On occasions these elements have been described in the Warthin tumor.[46,55] They may be related more closely to the adenocystoma mucipare and muco-epidermoid tumors.[55,92,95,96]

### *Submaxillary Salivary Gland*

The submaxillary glands included in this group could not be considered, in the strict sense of the word, normal. As previously noted, some of these glands were in the zone of lymph drainage from carcinomas of the face, mouth, or lips; others were examples of chronic sialadenitis. Accordingly, these glands could be expected to have a greater degree of lymphocytic infiltration than would be found in strictly normal glands. The degree of lymphocytic infiltration was graded from 0 to 3. Cases graded 0 exhibited very few lymphocytes, and those graded 3 showed germinal centers. Seventy per cent of the 50 submaxillary salivary glands examined were classified under 0, 18 per cent as 1, and 8 and 2 per cent as 2 and 3, respectively. The more extreme examples were cases of chronic sialadenitis. Unlike the findings in the parotid gland, no lymph nodes or encapsulated lymphoid aggregates were found.

In nearly all instances, the lymphocytic infiltrations, when present, were periductal and of an ill defined nature.

This group of glands included one with dilated ducts lined by tall, non-ciliated, eosinophilic, columnar epithelium. Low papillations projected into the lumina (Fig. 15).

In contrasting the groups of parotid and submaxillary salivary glands examined, two distinct differences were apparent. In the parotid gland, lymph nodes and encapsulated lymphoid aggregates were relatively common, whereas no such structures were observed in the submaxillary glands. Small, ill defined, periductal aggregates of lymphocytes were noted frequently in the parotid gland, but were relatively uncommon in the submaxillary gland except in instances of obvious chronic inflammation. The basic difference in the character of the two glands corresponded closely with the findings in the embryos. Oxyphilic granular cell variation in the ductal epithelium was not as pronounced as in the parotid glands.

## Branchiogenic Cysts and Fistulas

The branchiogenic derivatives examined were all from the area anterior to the sternocleidomastoid muscle, and near or below the ramus of the mandible. The primary interest in these structures was in the character of the epithelium. In all but 9 of the 50 examples, the epithelium was wholly of stratified squamous type. In 9 specimens, the cysts or fistulas were lined in part by stratified squamous and in part by pseudostratified, ciliated, columnar epithelium, or by pseudostratified, ciliated, columnar epithelium alone. There were no similarities, either in staining qualities or in nuclear arrangement, between the columnar epithelium of the branchial cysts and fistulas, and that of the Warthin tumor.

Berner[55] criticized the branchiogenic concept of the origin of the papilliferous cystadenoma lymphomatosum on the basis that the parotid anlage in no way comes in contact with the pharyngeal pouches. One case in our material presented a branchial fistula lined by respiratory and stratified squamous epithelium, which extended through the lower pole of the parotid gland. The histologic features of this structure are distinctly different from those of the Warthin tumor.

## Morphology

It would be repetitious to describe in detail each of the 23 cases of papilliferous cystadenoma lymphomatosum in this series. In the presentation that follows, it is our purpose to review some of the characteristics of the neoplasm, and to take exception to some of the previously

recorded statements. It is intended to emphasize those histologic features that are of importance from the point of view of histogenesis.

The gross findings in our series were limited to the 9 University Hospital cases. The factual data agreed with the characteristics of the neoplasm as recorded in the literature. As others have noted, there was no constant relationship between the duration of symptoms and the size of the tumor. None of the neoplasms reached the size of the tumor described by Callender[97] in 1929. All of the tumors were unilateral.

A thin fibrous capsule surrounding most of these neoplasms could be identified in the microscopic sections. In the one exception (case 6), the neoplastic tissue appeared to extend into the normal parotid gland. These tumors consisted, as a rule, of an admixture of papilliferous epithelial elements lining cysts and of lymphoid stroma. In the solid epithelial areas, the epithelium was in a medullary and/or tubular pattern. The epithelial cells were usually of a tall, columnar, eosinophilic variety, with a basal layer of polyhedral cells (the type seen in many of the adenomas). These have been designated as oxyphilic granular cells,[83] oncocytes,[35] or pyknocytes.[93] These cells were not an invariable finding, as all variations could be demonstrated including cells that compared favorably with the usual parotid ductal epithelium. The average cell tended to have opaque homogeneous-appearing cytoplasm in hemalum and eosin preparations. In many instances fine and coarse pink granules were apparent. The granules stained either greenish gray or red in Masson trichrome preparations. Case 3 presented an extremely granular epithelium. In hemalum and eosin preparations, the staining characteristics varied from pale pink in "healthy" cells, to an orange-red in cells undergoing retrogressive change.

In approximately one-third of the cases there could be seen occasional, and in 2 instances numerous, epithelial cells almost entirely devoid of cytoplasmic granules (Fig. 16). The cell-outlines and nuclear details were well preserved. This feature was exemplified to an extreme degree in case 9. These cells contained no stainable lipid in the sudan III stain. The nuclei of the epithelial cells were oval as a rule, and located in the luminal one-third of the cell body. In the columnar cells the long axis of the nucleus usually was vertical, and in the polyhedral cells the long axis, in the majority of instances, was horizontal with reference to the basement membrane. In the latter cells, the nucleus occasionally was spherical. There was usually a visible nucleolus, and the chromatin was finely clumped.

The secretory activity of the epithelial cells aroused much interest, primarily because of the reported presence of intercellular secretory

capillaries.[23,45] The secreted material was chiefly of a pink granular quality in the hemalum and eosin preparations. Occasionally, rounded eosinophilic masses of secretion were present. In well preserved areas, the secreted material appeared to arise as rounded masses from the free surface of the superficial epithelial layer (Fig. 17). In the Masson trichrome preparations, such masses stained varying shades of green to brown. Later in their evolution, the secreted masses broke away from the surface of the cell and presented the characteristic granular appearance. Scattered at irregular intervals, and occasionally grouped in twos, threes, or fours, epithelial cells were seen in which the nuclei were pyknotic and deeply staining (Fig. 18). The cytoplasm of these cells stained a deep pink in contrast to the surrounding epithelium. With the Masson trichrome technic, such cells stained deep orange or red, and were delineated sharply from the neighboring epithelial elements. These cells were narrow as if horizontally collapsed, and in instances the attenuated basilar portion extended to the basement membrane. On occasion they were seen in the process of being extruded into the lumina of the cystic spaces (Fig. 19), after which they constituted a part of the secretion-complex. This feature has been described as epithelial secretion occupying secretory capillaries.[23,45] The presence of pyknotic nuclei negates this interpretation.

In the series of Warthin tumors available for study, the characteristics of the epithelium ran the gamut of the variations apparent in the ducts of normal parotid glands. Epithelium was seen that compared favorably with the usual ductal epithelium (Fig. 20), through the types characterized by Hamperl[35] as "Übergangsformen," to well developed oxyphilic granular cells or oncocytes (Fig. 21). The "clear cell" variation of the oxyphilic granular cell (Figs. 16 and 18) also was found in some cases (7 and 9). As a general rule, the epithelium was arranged in two layers, a superficial columnar type and a second row of polyhedral cells. In some areas the epithelium consisted of more than two layers. Metaplasia of the usual columnar epithelium to stratified squamous occurred, but was rare. Ciliated epithelium was not observed.

The supporting lymphoid tissue showed the essential characteristics of a lymph node (cortex, lymph sinuses, and capsule) in some cases (Fig. 22). Sections of a neoplasm selected to demonstrate these findings, should be those taken through the capsule with a sufficiently adequate zone of uninvolved lymphoid tissue to make demonstration of these characteristics possible. When the epithelial portion of the tumor extended to the capsule with only small islands of lymphoid tissue apparent, these characteristics were obliterated. Consequently all of the

tumors were not satisfactory for the demonstration of these manifestations. The medulla usually was not apparent, as it was occupied for the most part by the epithelial portion of the neoplasm. In evaluating the lymphnodal component of the tumor, it was found desirable to utilize lymph nodes from the parotid gland as controls.

In the majority of cases, areas of inflammation were present, which were apparently secondary to the retained epithelial products in the cystic spaces. These areas were characterized by the presence of polymorphonuclear eosinophilic and neutrophilic leukocytes, plasma cells, histiocytes, and scar tissue (Fig. 21). The lymphoid tissue in the neoplasm tended to show the same propensity for fibrous connective tissue formation that had been noted in the lymph nodes of the parotid glands of older individuals. The scar tissue in these tumors tended to occupy a position parallel, and immediately adjacent, to the epithelium lining the cysts. In case 8 (Fig. 23) a polypoid mass of young scar tissue was protruding into one of the cysts. In addition there were hyalinized areas of old scar tissue. Manipulation of these masses by the patient may have contributed to some of these findings.

In summary, the histologic features agree with those previously described with certain exceptions. Neither cilia nor secretory capillaries can be demonstrated in our cases. The character of the epithelial cells shows a gradient from those closely similar to the usual parotid ductal epithelium, to the large granular and clear types of oxyphilic granular cells. There is also a variation in the degree of epithelial proliferation. The majority of cases present cysts lined by epithelium two layers in thickness; others exhibit exuberant cellular proliferation with secondary papillae. It is our conclusion that the epithelial cells secrete granular material into the lumina of the cysts and, on reaching what might be termed maturity, are extruded into the cystic spaces. The lymphoid portion of the neoplasm is derived from a lymph node or an encapsulated lymphoid aggregate, which is supplemented later by an inflammatory component.

## Histogenesis

The embryologic development and certain of the histologic characteristics of the submaxillary and parotid salivary glands have been considered. There is no feature of the papillary cystadenoma lymphomatosum for which the homologue has not been demonstrated in the parotid gland. All gradations have been observed, from ducts with lumina altered but little, if any, and lined by the usual epithelial cells, oxyphilic granular cells, or combinations of these types, to varying degrees of ductal dilatation with papillae of oxyphilic granular cell epithelium.

These variations have been more striking in the intralobular ducts of the parotid gland but have not been unusual in the interlobular ducts. On occasion oxyphilic granular cells are found in nests. The cellular pattern varies from simple medullary clusters to tubular formations. Foci are seen in which the pattern is mixed (Fig. 24). These clusters are situated usually in gland lobules, and vary in size from small nests to masses satisfying the requirements for a neoplasm. The latter extreme has been termed an oxyphilic granular cell adenoma or a type of oncocytoma.[83] The pure epithelial areas of many of the Warthin tumors (Fig. 25) consist of solid masses of somewhat polyhedral eosinophilic cells, that exist in medullary nests and demonstrate a tendency to form tubules. These areas present a histologic picture almost identical with some of the oxyphilic granular cell adenomas. The epithelial component of the papilliferous cystadenoma lymphomatosum differs, in general, from the pure adenoma only in the pattern of growth. These observations are believed to show the relationship between the two neoplasms, and to denote that the ductal epithelium, primarily at the intralobular level, contributes to the origin of both neoplasms.

That the epithelium in the majority of Warthin tumors is of the oxyphilic granular cell type is considered to be fortuitous. This alteration in the epithelium is not a neoplastic prerequisite, as all possible epithelial variations have been observed in the tumors examined. The age range in which the neoplasm occurs may contribute to the preponderance of oxyphils.

In approaching the fully differentiated papilliferous cystadenoma lymphomatosum, it may be well to consider a tumor believed to occupy a position between that neoplasm and the simple inclusion of ducts in lymph nodes. This may be considered a variant of the Warthin tumor, as it somewhat resembles case III of Gaston and Tedeschi.[62] Our case 12307-LAZ is an example of a polycystic parotid tumor with lymphoid stroma (Fig. 26), in which the multi-layered lining epithelium consists of a surface layer of cuboidal cells with the same staining characteristics as the usual ductal epithelium. In areas the epithelium is flattened to such an extent that it is not unlike stratified squamous epithelium. There is an ill defined papilliferous pattern. Such a tumor may be representative of some others included with the Warthin tumors in the literature.[8,18]

As noted in the control material, the mixture of epithelial and lymphoid elements characteristic of the papilliferous cystadenoma lymphomatosum was observed only in the parotid gland, and its immediate vicinity. Such structures were not observed in relation to any of the

other major salivary glands. If salivary gland ducts occur at all in lymph nodes in relation to the submaxillary and sublingual salivary glands, it must be considered a rare association. All of the Warthin tumors included in this report and in respect to which location was given, were located in the parotid gland or its immediate environs with 5 exceptions. It was implied that 4 of these were removed from the submaxillary salivary gland (Spitznagel,[5,32] Gödel,[5,32] Wendel,[34] and Steinhardt[35]). Albrecht and Arzt[1] reported one from the submaxillary region, but the relationship was not considered sufficiently definitive to permit tabulation as a tumor arising in the submaxillary gland. Martin and Ehrlich[26] did not accept the tumors of Albrecht and Arzt, Spitznagel, and Wendel as of submaxillary origin. "None of these authorities actually stated that the tumors were found in the substance of the submaxillary gland or attached to its anterior surface. The fact that they have not done so indicates that they have not appreciated the fact that the anteroinferior aspect of the tail of the parotid lies in contact with the posterior superior aspect of the submaxillary salivary gland, although the deep cervical fascia separates the two." It appears highly probable that all of these neoplasms arise in the parotid gland or its immediate vicinity. If any occur in the submaxillary gland, they may be expected to be histologically similar to the neoplasm reported by Steinhardt.[35] This tumor has been described as consisting of delicate papillae lined by cubical epithelium, chiefly in a single layer. His photomicrograph shows a relatively smaller quantity of lymphoid tissue than is seen in the usual case from the parotid region.

It seems apparent, therefore, that the Warthin tumor is the result of the neoplastic proliferation of ducts. These epithelial components are clothed in lymphoid tissue. The lymphoid tissue, in instances, exhibits the characteristics of a lymph node. Considering the histologic sections of the individual tumors alone, there is no clear evidence to disprove absolutely that in individual instances Warthin tumors may not arise in ducts outside of lymphoid tissue, with a secondary infiltration of lymphocytes on an inflammatory basis. The genesis of this inflammatory response has been described previously, and the possibility is supported by the fact that, on occasion, phagocytes in the surrounding stroma may contain material similar to that in the cystic spaces.

The normal function of the lymph node as a filter is impaired due to the interference with filtration by the included epithelial structures. The integral lymphnodal characteristics are distorted under these circumstances; however, they can be demonstrated in some instances if the tumor is fortuitously sectioned in such a way that these structural

manifestations are not concealed by the epithelial elements and the inflammatory response.

Some of the papilliferous lymphomatous cystadenomas occur within the parotid gland, and others outside of the gland proper in the vicinity of its capsule. Observations of the gland during its embryonal development explain the occurrence of the neoplasm in paraglandular locations. It has been noted that the parotid gland, unlike the submaxillary salivary gland, does not develop as a closely aggregated integral unit. When the capsule of the gland finally condenses at a later stage, lymph nodes at the periphery, into which ducts have penetrated, may be isolated outside the glandular area. In such cases the ducts penetrating the lymph nodes must be interrupted, with the lymph nodes retaining the distal portions. A neoplasm arising in such a lymph node would be located outside of the parotid gland proper.

## Discussion

Several concepts of the histogenesis of lateral congenital cysts of the neck have been proposed.

Wenglowski,[98] in 1912, following extensive embryologic and anatomical research, related the origin of cervical cysts and fistulae to a persistence of the thymic anlage and the thymopharyngeal canal. Delanglade *et al.*,[77] in 1914, described additional cases. These authors indicated the presence of elements having great similarity to Hassall's corpuscles. The spaces in these structures were described as lined by stratified squamous and ciliated columnar epithelium. The origin of such epithelial structures from remains of the embryonic pharyngeal pouches and gill furrows was proposed by some (Ssobolew,[11] Feldmann,[12] Askanazy,[20] Spitznagel and Gödel[32]), and from heterotopia of pharyngeal endoderm by others.[2]

Gaston and Tedeschi[62] considered that the lack of ciliated columnar epithelium in the Warthin tumor is not of importance in eliminating the sources of origin mentioned in the preceding paragraph. It seems apparent from our studies that it *is* an important factor. The cysts and fistulae from branchial remains are lined invariably by either stratified squamous or ciliated columnar epithelium. Among the Warthin tumors examined, there has not been a single convincing instance of cystic spaces lined by ciliated columnar epithelium, and squamous metaplasia is exceedingly rare. The same reasoning may be applied to the concept of arrested thymic anlage or the so-called thymopharyngeal canal. In addition, no structures resembling Hassall's corpuscles have been observed in the lymphoid tissue. The age incidence of patients consulting

physicians for branchial cysts and fistulae is decidedly different from that of those with Warthin tumors.

We believe that the theory advanced by Kraissl and Stout[24] which related the orbital inclusion or the "organ of Chievitz" to the Warthin tumor can be eliminated. If this structure contributed to the genesis of the Warthin tumor, such neoplasms should appear more frequently in the area medial to the masseter muscle and mandible, and more anterior than the parotid area. As far as can be determined, no papilliferous cystadenomata lymphomatosa have been reported in the area described.

The original concept of Robert Meyer[99] that epithelium-like linings of this type represent hypertrophic endothelium in diseased lymph nodes may be discounted. The epithelial nature of this portion of the tumor has been accepted generally.

The oncocytic concept of origin[23] does not adequately explain all of the features of the neoplasm, in that it does not account for the Warthin tumors in which the epithelial component is not of the oncocytic type. In addition, these cells have been described in other locations,[35,46] but Warthin tumors have been described only in the parotid area.

These neoplasms present a good prognosis, and, with rare exceptions, no other neoplasm has been described in the head and neck region of patients who bear them. Such considerations eliminate the possibility that these neoplasms are metastatic carcinomas.

It is our opinion that a careful microscopic evaluation of any Warthin tumor makes it possible to place the neoplasm in one of two histogenetic groups.

1. *Neoplasms arising from parotid ductal epithelial elements included in lymph nodes,* such inclusion having been described previously by Neisse,[100] Löwenstein,[101] Lubarsch,[102] and Bairati,[103] and verified in our material. Neisse and Bairati have described similar structures in the submaxillary region. This is essentially the original concept of Albrecht and Arzt.[1] As these writers have indicated, histologic examination of the neoplasm reveals the close relationship between the parotid gland and the tumor. Small salivary gland ducts are found in the capsule of the neoplasm and in the neighboring stroma. There is a striking similarity of the epithelial elements of the neoplasm, and the epithelial lining of the ducts of the parotid gland. "Es liegt daher nahe, auf Grund dieser so innigen Beziehungen wenigstens für unsere Geschwülste eine histogenetische Beziehung zu den Speicheldrüsen als möglich anzunehmen, entweder so, dass bei der ersten Differenzierung der Speicheldrüsen aus dem Entoderm der Mundbucht Gewebskeime der Speicheldrüsen aberriert und dann in Lymphknoten eingeschlossen worden

wären, . . . . Somit stellen unsere beiden Fälle gewiss zwei Beispiele von Gewebsverirrung oder Dystopie, wie dies R. Meyer neuerdings bezeichnet . . . ."

2. *Tumors due to the neoplastic proliferation of parotid ductal epithelium and the concomitant accumulation of lymphoid tissue in a manner previously described.* As indicated by some,[26,62] one of the primary objections to the first concept is that essential lymphnodal characteristics cannot be demonstrated, and for this reason it has been denied that the lymphoid elements represent lymph node. It is our contention that these characteristics can be demonstrated. It is agreed that there is a chronic inflammatory element in the stroma that is essentially of a lymphocytic nature. The propensity of the major salivary glands to develop lymphocytic accumulations in the stroma has been indicated by others.[28] Some have stated that the presence of the oxyphilic granular cell variation *per se* stimulates the accumulation of lymphoid elements.[35] It is our opinion that the collections of lymphocytes ordinarily seen around ducts as part of the process of inflammation contribute to the bulk of the neoplasm and aid in the distortion of the normal lymphnodal architecture. Study of some of these neoplasms in their early formative stages justifies the inclusion of this second group. The lymphoid tissue of these small neoplastic proliferations resembles that in some of the fully developed tumors, in that lymphnodal characteristics cannot be demonstrated. The epithelial elements, in these instances, develop in an aggregate of lymphoid tissue. As the tumor expands and the parenchyma of the glandular lobule undergoes atrophy, the trabeculae condense as a capsular structure around the periphery.

## Summary

The development of the major salivary glands was studied in 18 embryos varying in crown-rump length from 20 to 200 mm. (7 to 21 weeks). Structural features were re-examined in 100 normal parotid glands from patients ranging in age from 7 months of gestation to 75 years; and in 50 submaxillary glands derived chiefly from patients in the fifth and sixth decades. Fifty branchiogenic cysts and sinuses from patients ranging from 4 to 40 years were examined also. Finally 23 examples of papilliferous cystadenoma lymphomatosum were studied.

The following conclusions have been derived from this study: The papilliferous cystadenoma lymphomatosum and the oxyphilic granular cell adenoma are related neoplasms that differ only in pattern and supporting stromal elements. Both neoplasms are derivatives of the epithelium of the excretory duct radicles of one of the major salivary glands. The Warthin tumor is considered to be a neoplasm of the pa-

rotid salivary gland and its immediate vicinity. The origin of this tumor is (1) in the neoplastic proliferation of parotid ducts included in lymph nodes. This opinion is based primarily on the finding that lymph nodes containing ducts have been observed, without doubt, only in the parotid gland area. The essential lymphnodal characteristics of the lymphocytic collections can be demonstrated in selected cases of neoplasm. (2) After origin of the neoplasm in the ductal epithelium of the parotid gland, the lymphoid tissue may be that of an inflammatory lymphoid aggregate.

The intimate relationship between the inferior portion of the parotid gland and the posterior portion of the submaxillary gland may be responsible for erroneously attributing neoplasms occurring in this area to the submaxillary gland.

That oxyphilic granular cells or oncocytes constitute the epithelial component of the Warthin tumor in the majority of cases is not considered to be of primary significance. It is thought that this epithelial variant does not constitute a neoplastic prerequisite, although this type of epithelium may be more disposed to neoplastic change than is the usual ductal epithelium.

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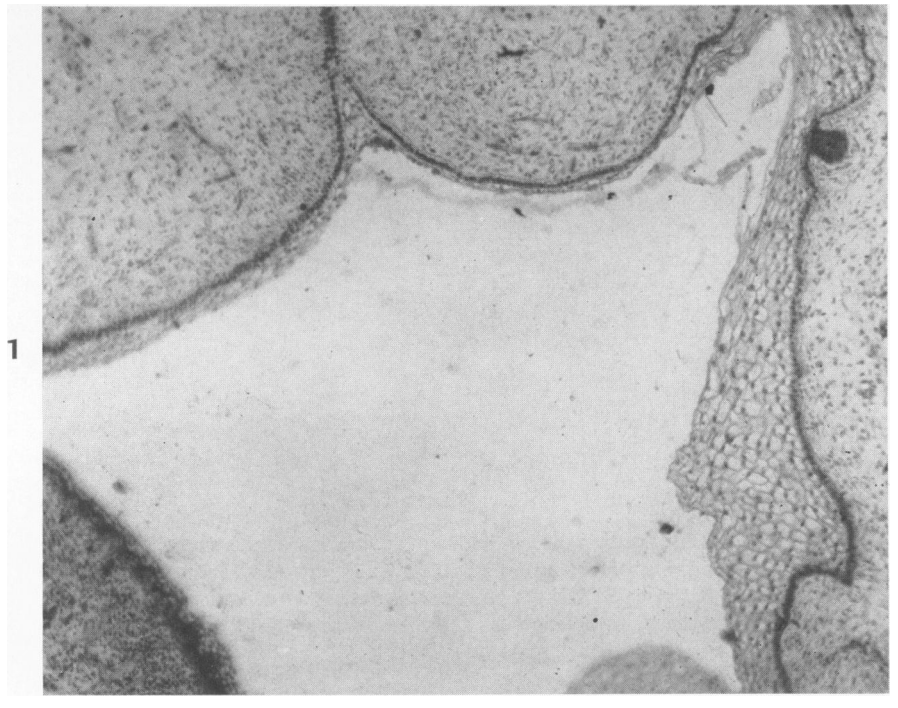
[ *Illustrations follow* ]

## DESCRIPTION OF PLATES

### PLATE 110

FIG. 1. A frontal section through the head of a human embryo (crown-rump length, 58 mm.). The orbital inclusion may be seen in the upper right corner as a small, dark knob of cells arising from the buccal sulcus. The mass in the lower left corner is the lateral superior portion of the tongue. Hemalum and eosin stain. × 100.

FIG. 2. A frontal section through a more anterior area of the embryo illustrated in Figure 1. The origin of the parotid gland is represented by the bud of dark staining cells arising from the buccal sulcus in the upper right corner of the illustration. The lateral superior surface of the tongue may be seen in the lower left corner. Hemalum and eosin stain. × 100.



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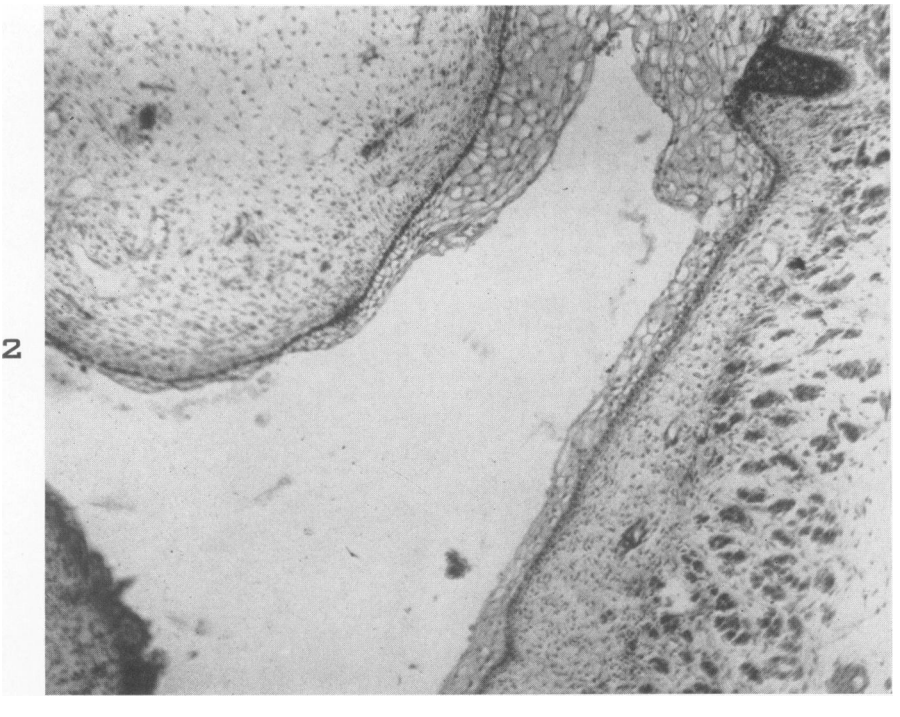

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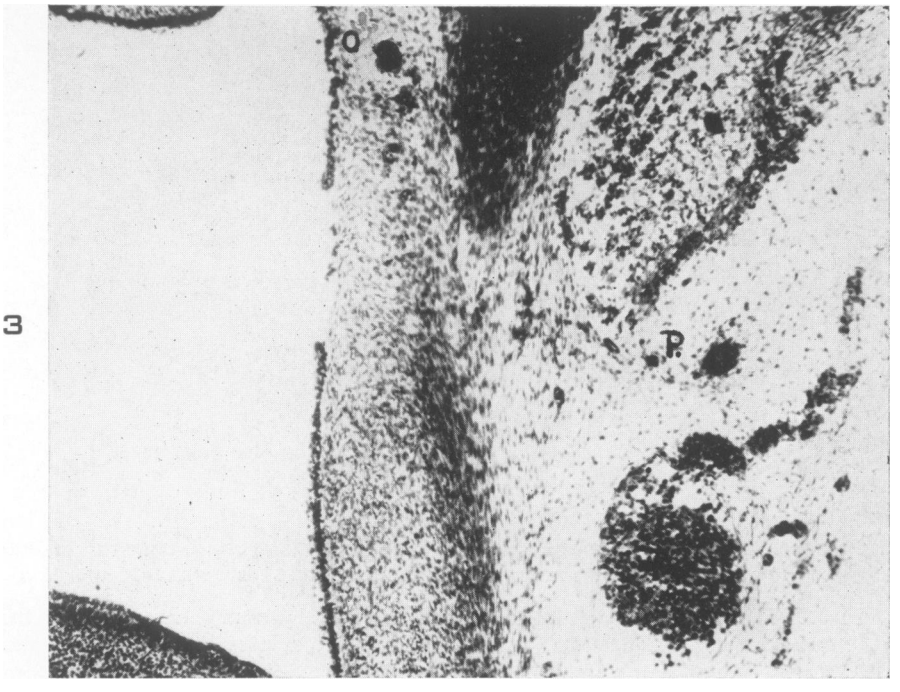
Bryant and Thompson Histogenesis of Papillary Cystadenoma Lymphomatosum

## PLATE III

FIG. 3. A frontal section of an embryo (c.-r.l., 28 mm.) through an area more posterior than that of either Figure 1 or Figure 2. O indicates the orbital inclusion lying medial to the muscles of mastication, and the small, dark mass near P is the parotid which has assumed a more lateral position. The lateral superior margin of the tongue may be seen in the lower left corner. Hemalum and eosin stain. × 100.

FIG. 4. Parotid ducts included in a lymph node from the parotid region of an embryo of 200 mm. crown-rump length. Hemalum and eosin stain. × 100.

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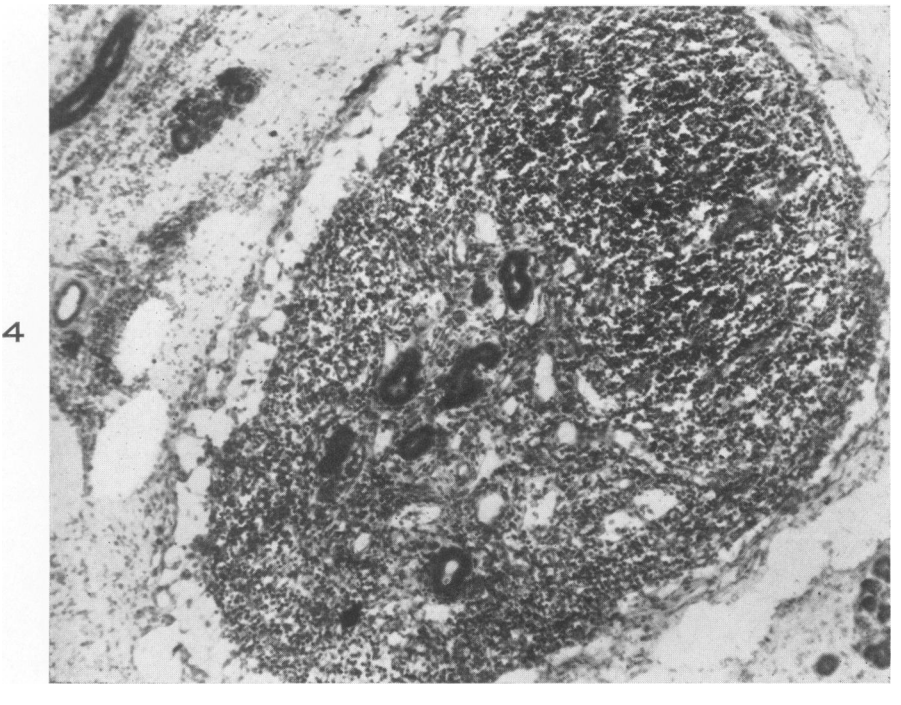


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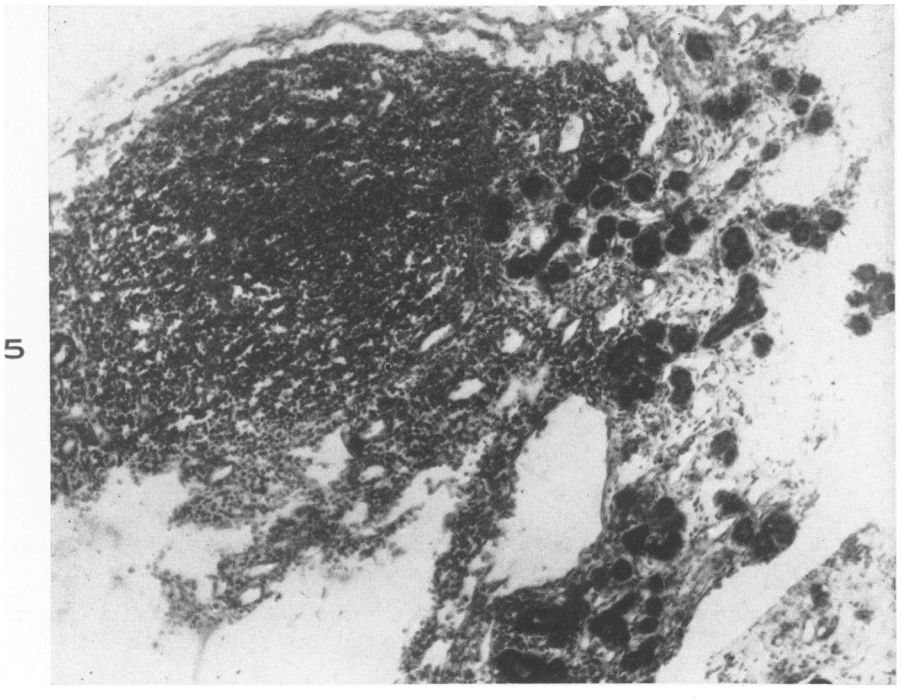
Bryant and Thompson Histogenesis of Papillary Cystadenoma Lymphomatosum

PLATE 112

FIG. 5. Parotid ducts included in a lymph node from the parotid region of an embryo of 105 mm. crown-rump length. Hemalum and eosin stain. × 100.

FIG. 6. The submaxillary gland of an embryo (c.-r.l., 58 mm.), demonstrating the tendency of this gland to be encapsulated and to develop as an organized unit. Hemalum and eosin stain. × 100.



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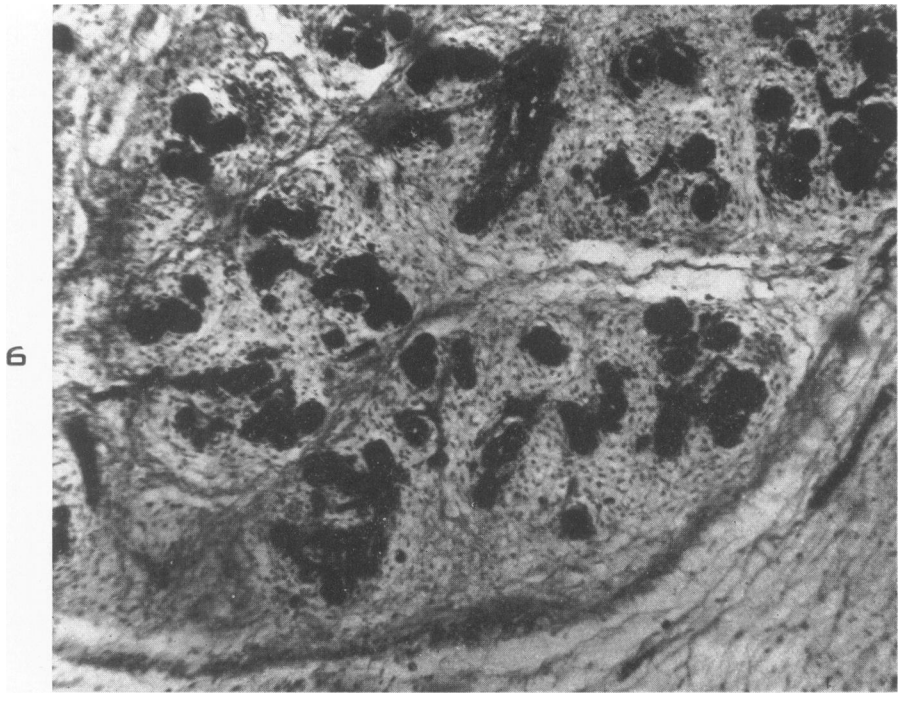

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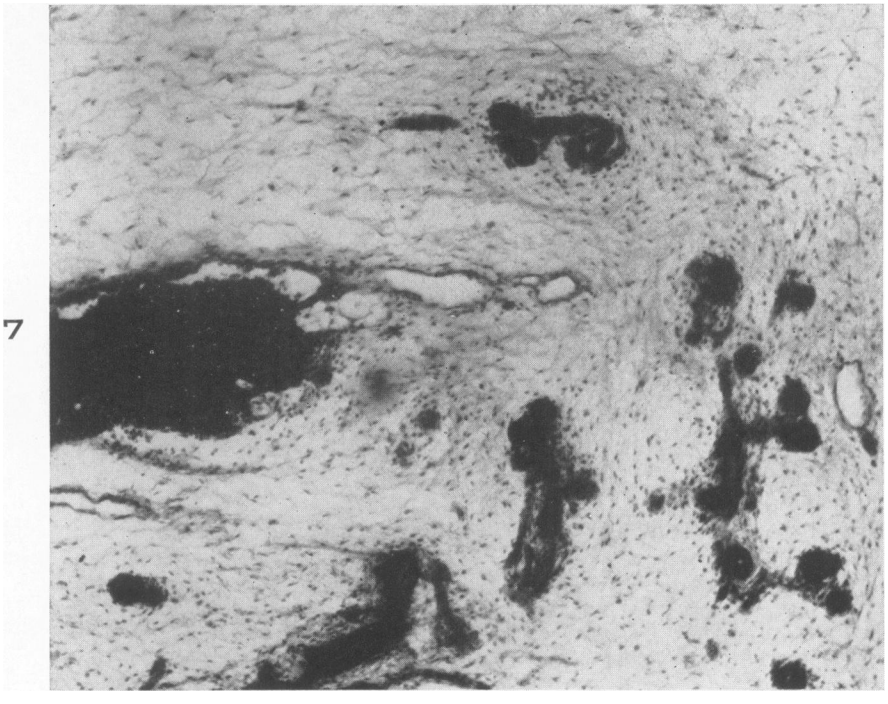
PLATE 113

FIG. 7. The parotid gland from the same embryo illustrated in Figure 6. The absence of a capsule may be noted, as well as the "sprawled out" appearance of the developing parenchyma. Hemalum and eosin stain. × 100.

FIG. 8. Parotid ducts in a lymph node from the parotid gland region of a fetus in the seventh month of gestation. Hemalum and eosin stain. × 200.

FIG. 9. Parotid ducts in a lymph node from the parotid gland region of an adult. Hemalum and eosin stain. × 240.



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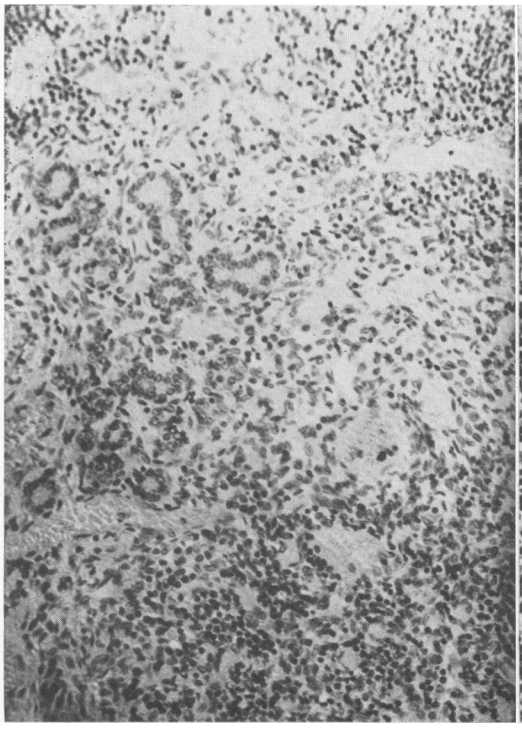

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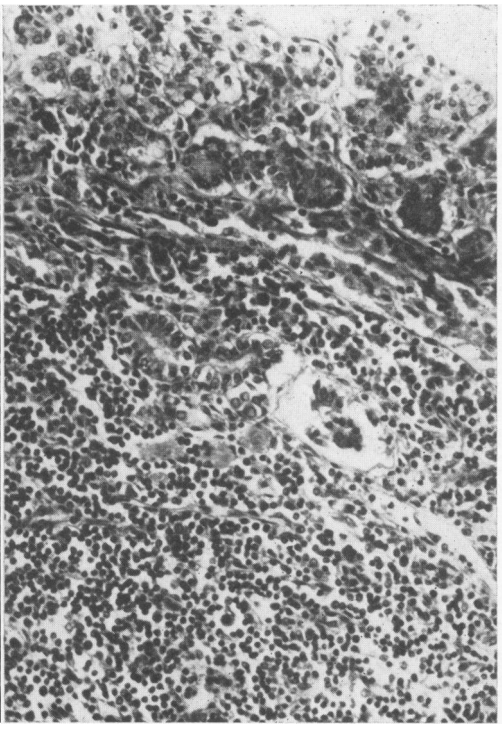

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PLATE 114

FIG. 10. Parotid ducts in a lymph node from the parotid gland region of an adult. This is an area from the preceding figure at a higher magnification. Hemalum and eosin stain. × 550.

FIG. 11. A lobule of parotid gland extending into the hilus of a lymph node, from an adult. Hemalum and eosin stain. × 200.

FIG. 12. Parotid ducts showing a transition of the usual type of epithelium to the oxyphilic granular type. Hemalum and eosin stain. × 500.

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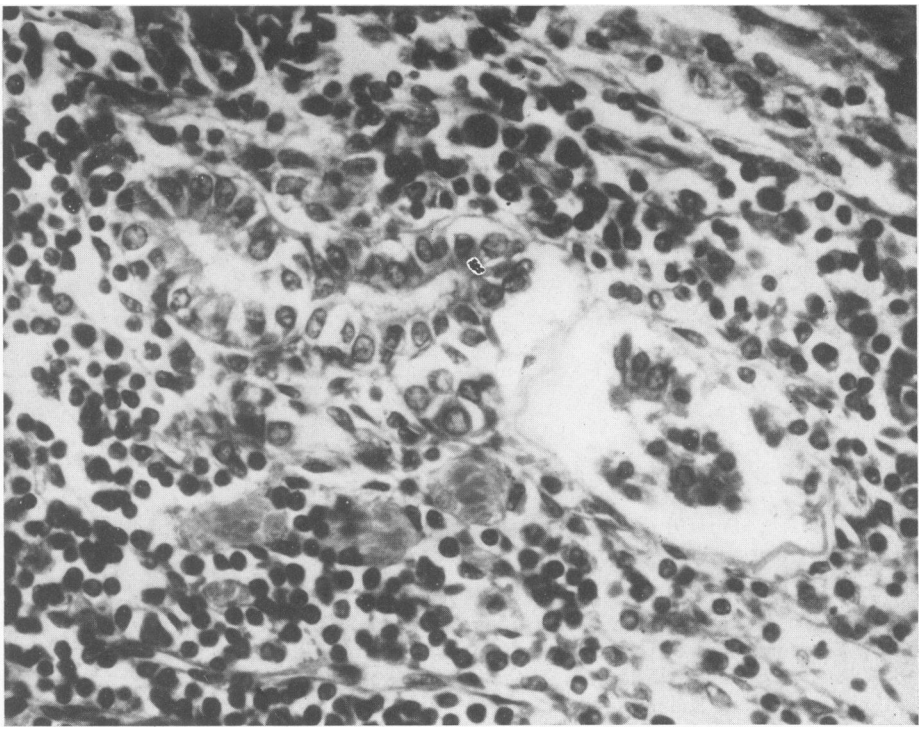

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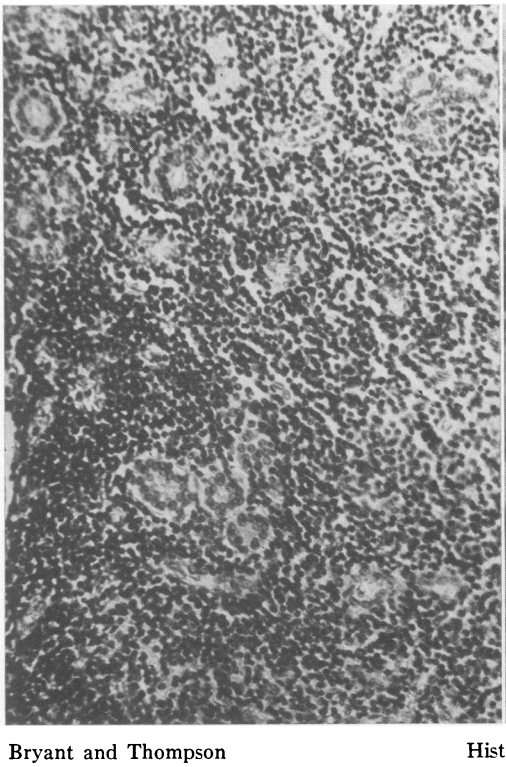

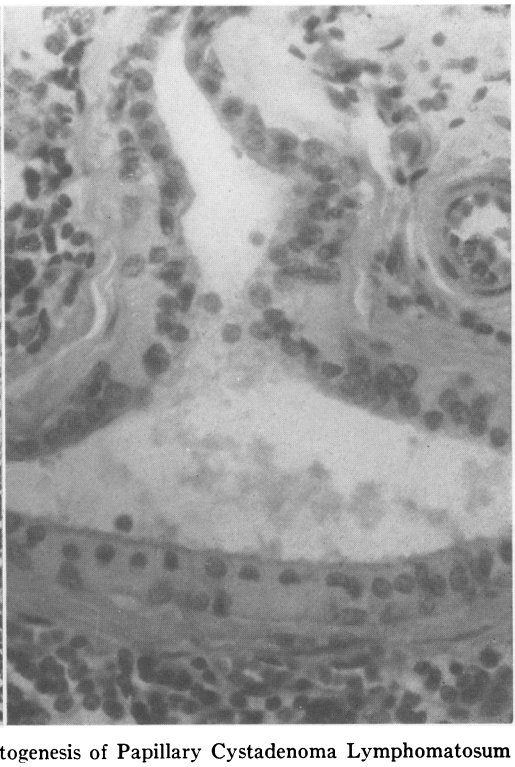

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## Plate 115

Fig. 13. Parotid ducts showing transition of the epithelium to the oxyphilic granular type. Hemalum and eosin stain. × 500.

Fig. 14. Parotid ducts lined by the "clear cell" variant of oxyphilic granular cells. The nuclei of the cells forming the ductal epithelium are located in the luminal one-third of the cell body. In acinar cells of a somewhat similar appearance, the nuclei are located in the basilar one-third of the cell body. Masson's trichrome stain. × 500.

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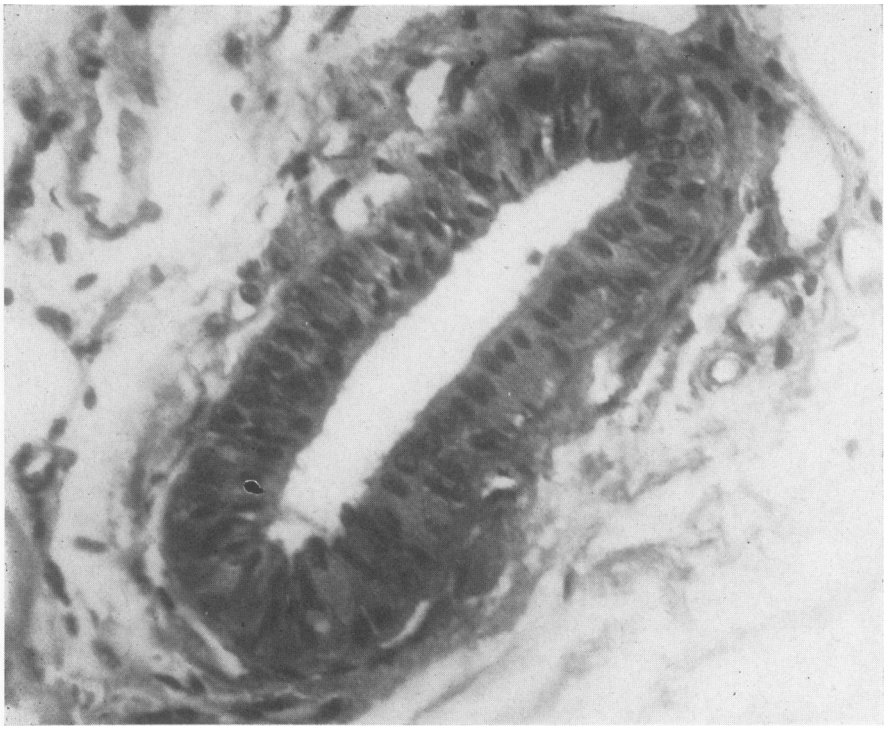

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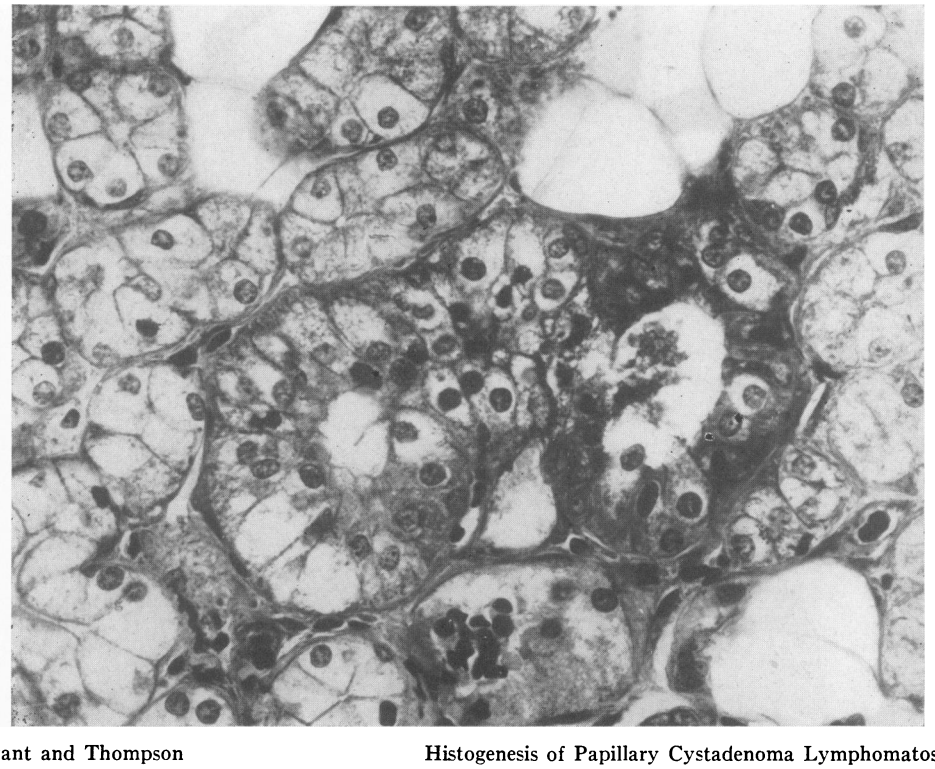

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PLATE 116

FIG. 15. A dilated interlobular duct of the submaxillary gland. The epithelium consists of oxyphilic granular cells, and low papillations project into the lumen. The similarity of this epithelium to that of the Warthin tumor and of the oxyphilic granular cell adenoma may be noted. Hemalum and eosin stain. × 200.

FIG. 16. "Clear cells" of the epithelial component of the Warthin tumor. Masson's trichrome stain. × 500.

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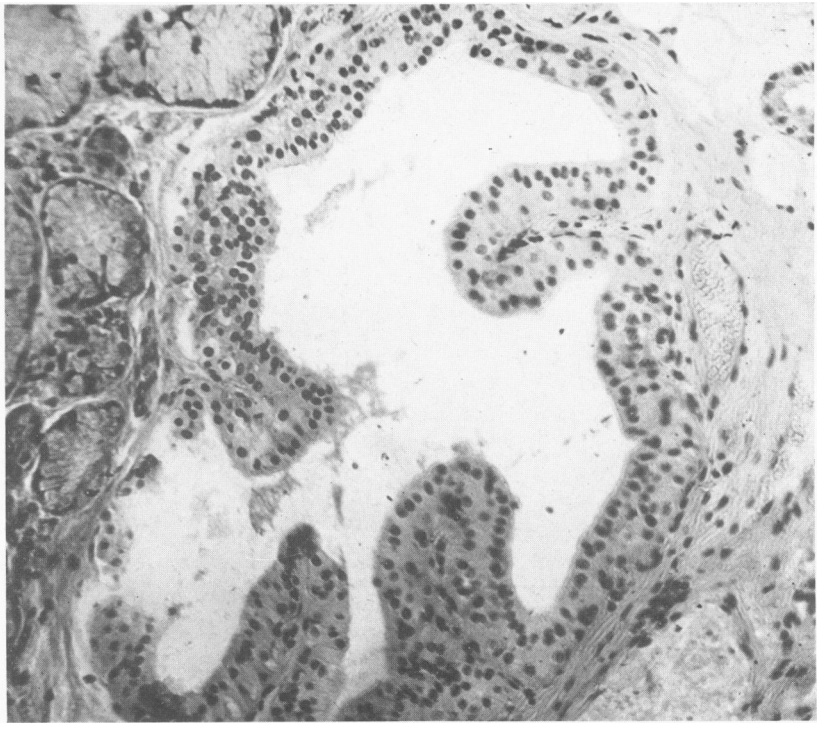

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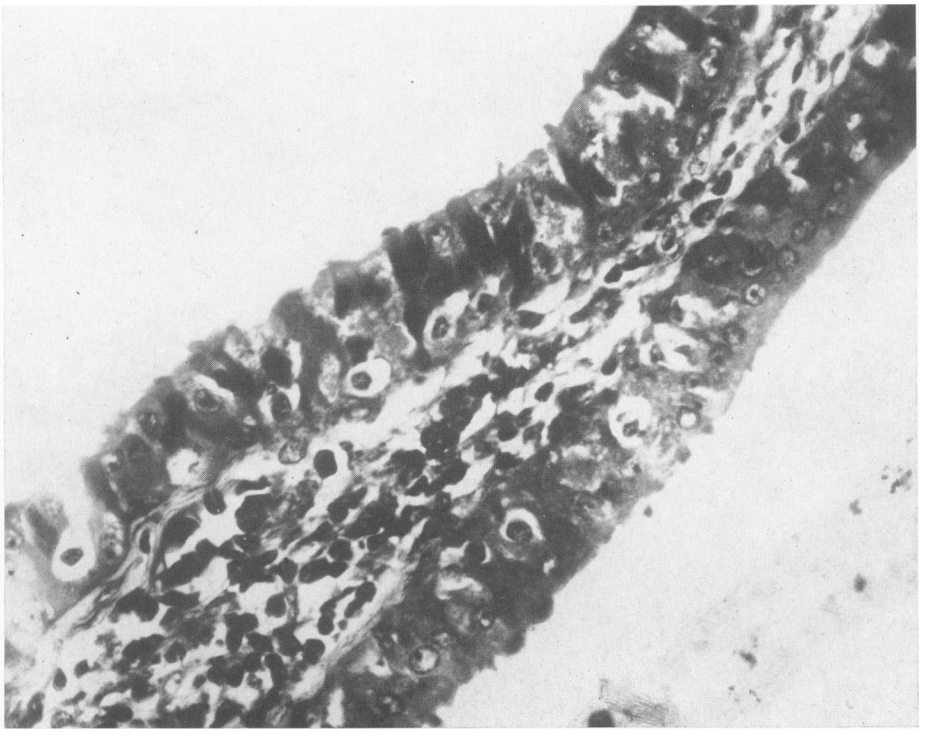

Bryant and Thompson Histogenesis of Papillary Cystadenoma Lymphomatosum

PLATE 117

FIG. 17. Small masses of secretory material may be seen arising from the luminal surface of the epithelium of a Warthin tumor. Masson's trichrome stain. × 500.

FIGS. 18 and 19. Collapsed, sharply delineated cells with pyknotic nuclei among the epithelial cells of a Warthin tumor. These cell bodies are seen forming part of the secretion of these tumors. Masson's trichrome stain. × 500.

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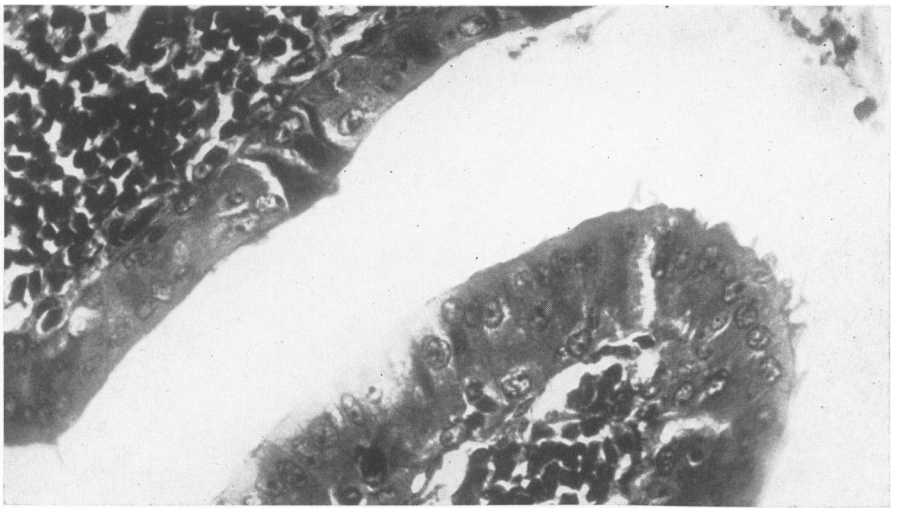

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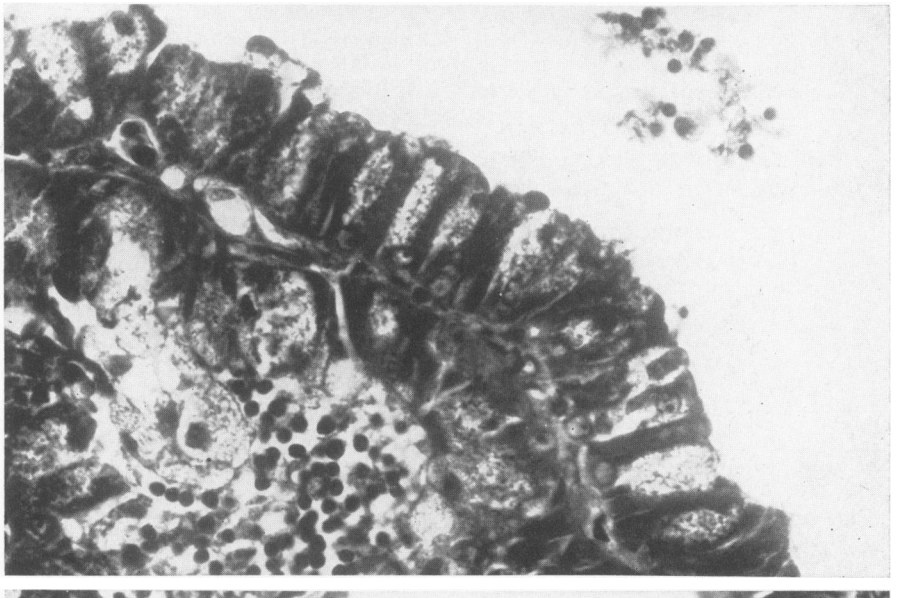

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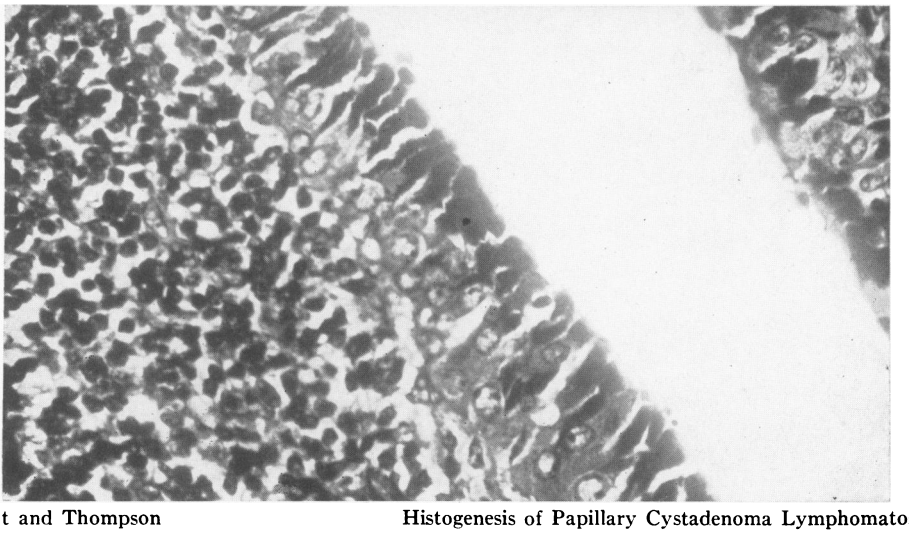
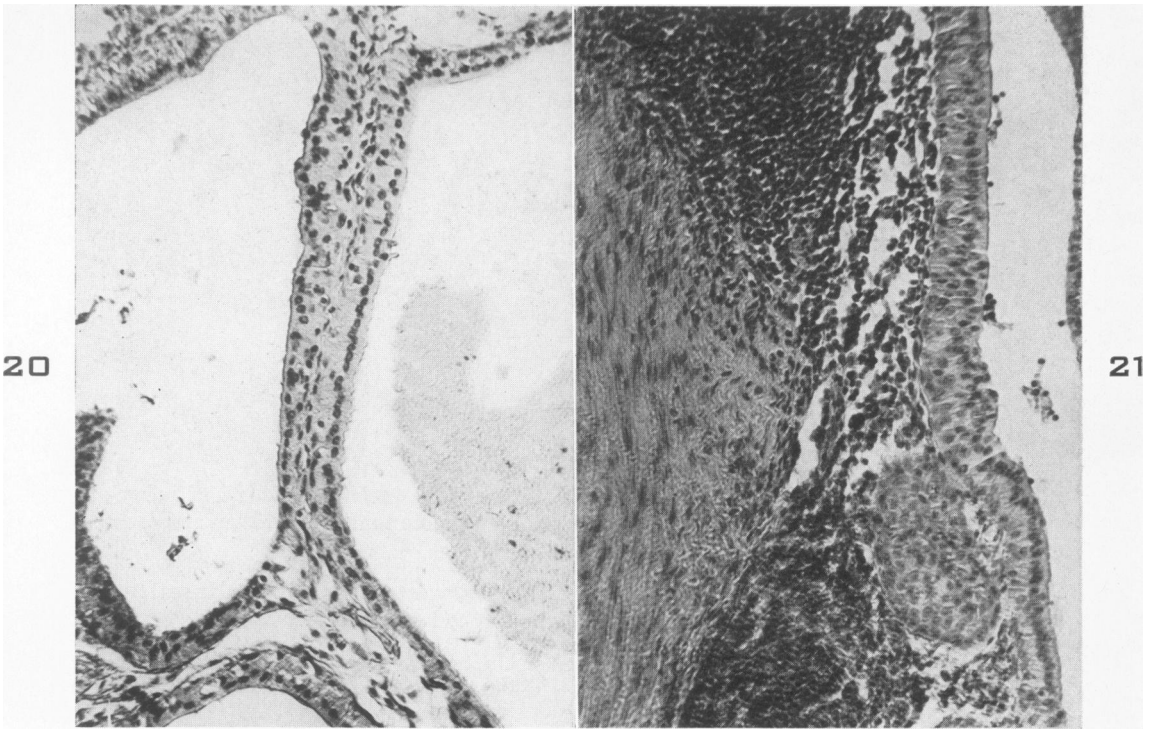


PLATE 118

FIG. 20. An area from a Warthin tumor showing epithelium that compares favorably with that of the usual parotid ductal epithelium (lower portion of the photograph). Stages in the transition to the oxyphilic granular cell type are seen. Hemalum and eosin stain. × 200.

FIG. 21. Oxyphilic granular cells, backed by scar tissue and an inflammatory infiltration, lining cystic spaces of a Warthin tumor. Hemalum and eosin stain. × 200.

FIG. 22. Peripheral lymph sinuses beneath the capsule and extending into the supporting stroma of a Warthin tumor. Hemalum and eosin stain. × 100.



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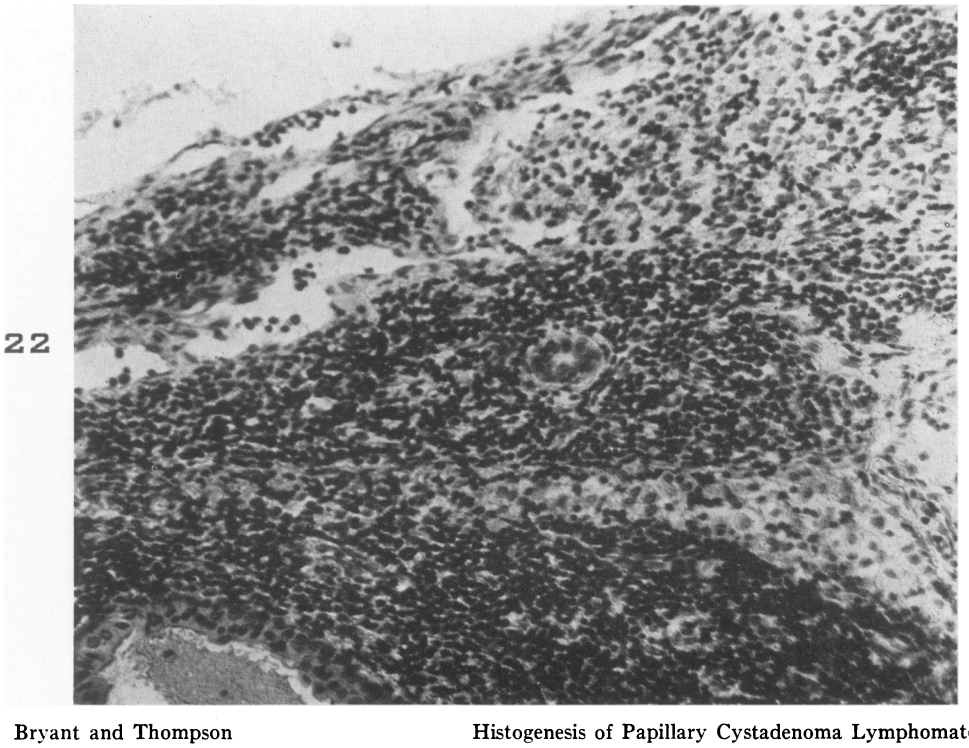

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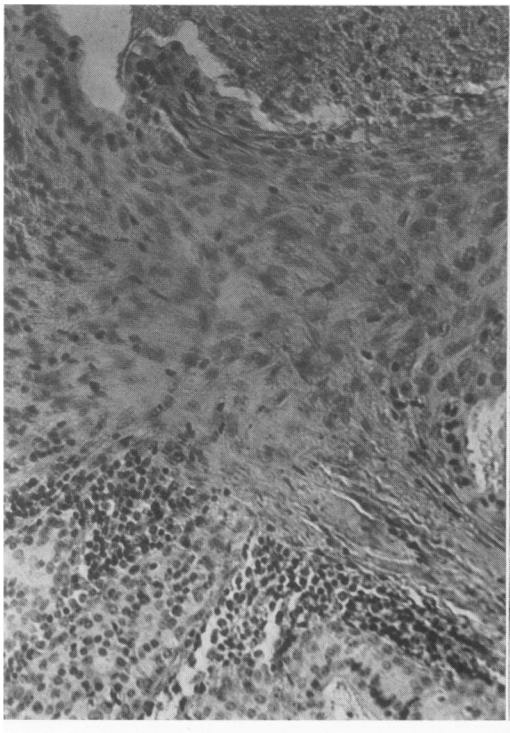
## PLATE 119

FIG. 23. A polypoid mass of young scar tissue and associated products of inflammation protruding into a cystic space of a Warthin tumor. Hemalum and eosin stain. × 200.

FIG. 24. A focus of oxyphilic granular cells forming medullary and tubular patterns in a lobule of the parotid gland. Hemalum and eosin stain. × 500.

FIG. 25. A solid epithelial area of a Warthin tumor. Hemalum and eosin stain. × 500.

FIG. 26. A portion of a cystic tumor considered to occupy a position between the simple inclusion of ducts in lymphoid tissue and the Warthin tumor. Hemalum and eosin stain. × 100.



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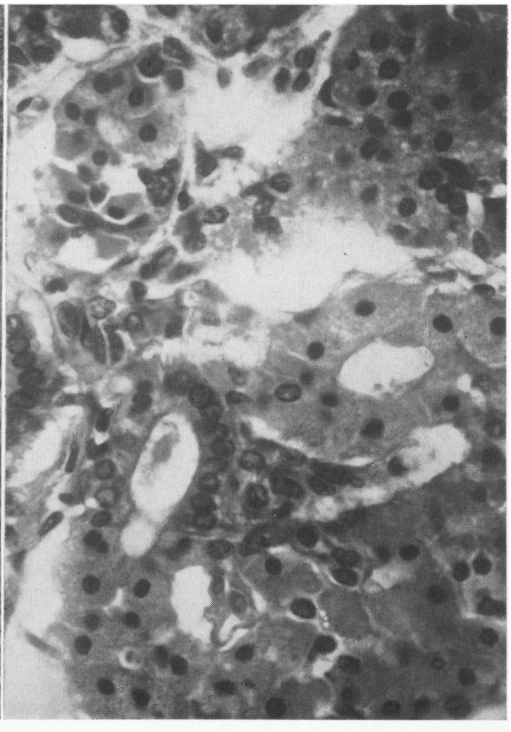

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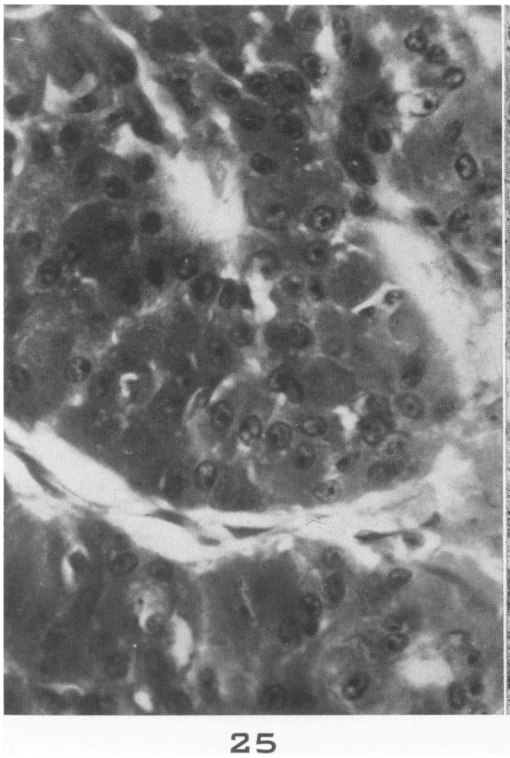

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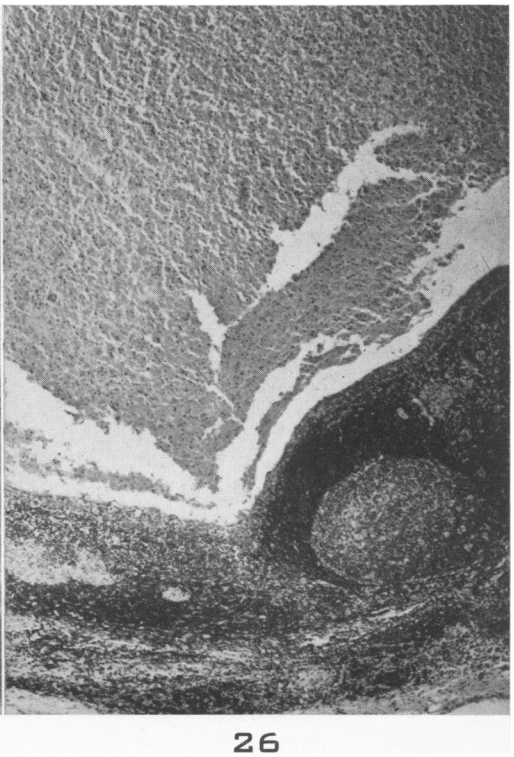

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