

SEBACEOUS GLANDS IN NORMAL AND NEOPLASTIC  
PAROTID GLANDS

POSSIBLE SIGNIFICANCE OF SEBACEOUS GLANDS IN RESPECT  
TO THE ORIGIN OF TUMORS OF THE SALIVARY GLANDS\*

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The presence of structures resembling sebaceous glands in two parotid glands that contained adenomas has been mentioned in another publication.<sup>1</sup> In those cases it was observed that such structures arose from the intralobular ducts. In one instance, sebaceous glands were seen in an area of tumor formation as well as in the normal parotid tissue. However, in the other they were present only in the normal portion. The glandular structures were in all respects similar to the sebaceous glands found in areas where they are not associated with hairs. Their occurrence in parotid glands is not mentioned in any of the standard textbooks of histology. Search of the literature revealed two reports in which similar findings have been recorded. Hamperl<sup>2</sup> observed holocrine fat secretion (sebaceous-like transformation) in the excretory system in four submaxillary glands of 4 of 85 persons from whom he studied the uvular, sublingual, and submaxillary glands, and in one parotid gland. Hamperl stated that he found sebaceous-gland-like transformation in small intralobular ducts ending blindly. The ages of the persons in whom this transformation was found in the submaxillary glands were 6½, 9, 20, and 36 years, respectively, and the person whose parotid gland showed the sebaceous-gland-like transformation was 6 years old.

The only other report of sebaceous glands in the parotid gland is that of Hartz.<sup>3</sup> The individual in whom they were found was a 34-year-old woman who had a recurrent mixed tumor of the left parotid gland. The tumor was removed with the surrounding glandular tissue. The microscopic study of the specimen showed a typical "mixed tumor" and some normal parotid gland in which Hartz found small sebaceous glands originating from the striated or intercalated ducts. He had the impression that the sebaceous glands developed from short branches that ended blindly. This author pointed out that it was not known whether such structures "were present before the tumor and the first operation or whether those abnormal circumstances were the stimulus for the peculiar differentiation of the ductal epithelium."

Because of these findings it was thought that further study was neces-

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sary to determine (1) whether sebaceous glands are present in normal parotid glands, (2) whether they are present in parotid glands which are the site of a neoplastic process, and (3) whether or not the occurrence of such structures in the salivary glands could have any bearing on the explanation of the tumors occurring in these salivary glands. With these questions in mind, it was decided to study normal parotid glands, and those in which tumors had occurred.

#### MATERIAL AND METHODS

The material for this study was divided into two groups: (1) tumors of the parotid gland around which there was normal salivary gland tissue, and (2) normal parotid glands obtained from autopsy material.

The first group consisted of prepared sections from 249 tumors of the parotid gland of which only 133 showed some normal salivary gland tissue about the tumor. These latter slides were used for the present study. With the exception of one case from Memorial Hospital, New York City, all came from the Department of Pathology of the University of Michigan. They represented the tumors of the parotid gland diagnosed during the preceding 15 years, which will be considered together and will be referred to as group 1 throughout this communication (Table I).

TABLE I  
*The Material of Group 1 (Tumor Cases) with Percentage of Those That Had Sebaceous Glands*

Number of tumors	249
Number of tumors with normal parotid gland attached	133
Number of cases with sebaceous glands	33
Percentage of cases with sebaceous glands of those with parotid gland attached	24.8

The amount of normal parotid tissue present varied considerably, but as a rule it was not very abundant. In order to be included in this study, it was required that at least one of the sections show 25 mm.<sup>2</sup> of normal salivary gland. All of the sections from this group were stained with hematoxylin and eosin.

The second group was composed of 100 normal parotid glands obtained from 51 persons who died from various causes, including accidents and violence. These were unselected individuals on whom autopsies were performed at the University Hospital. Their ages ranged from 7 months to 76 years. Thirty-three were males. Both parotid glands were available for study from 49 individuals and from each of 2, only one gland could be obtained. The amount of parotid tissue removed from each person was about two-thirds of each gland in most cases. Formalin was used to

fix 80 of the 100 parotid glands and the remaining 20 were fixed in absolute alcohol. An average of two blocks of tissue were imbedded in paraffin from each gland and five sections obtained from each block were stained with hematoxylin and eosin. Hortega's silver carbonate nuclear stain on frozen sections<sup>4</sup> was done in every case in which sebaceous glands were found, provided the material had been fixed in formalin. This was followed by scharlach R staining for fat in every section which showed sebaceous glands in the silver impregnation. Mayer's mucicarmine stain was used on material fixed either in formalin or in alcohol, and Best's carmine stain when the sections showed sebaceous glands and the material had been fixed in absolute alcohol.

#### MICROSCOPIC FINDINGS

The microscopic findings were similar in both groups. The parotid glands presented the normal tubulo-acinar structure and they varied only in degree of atrophy, as recorded in Table II. Most of the ducts were normal, but in areas changes had taken place in some branches of the striated ducts or more frequently in the intercalated ducts. These branches or ducts usually were short and had blind ends, instead of branching normally into intercalated ducts or ending in glandular acini. The blind ducts were lined by low-cuboidal epithelium that progressively changed into the stratified squamous type. This change was sometimes very abrupt.

Some of these ducts were curved, forming small hooks which often ended in saccular or alveolar epithelial structures which varied in size from 50 to 350  $\mu$ . They were spherical, ovoid, or elongated, and were composed of a well defined basal membrane over which lay a row of cuboidal or flattened epithelial cells (Figs. 1 to 8). Sometimes these cells formed small groups composed of several layers situated about the periphery of the alveolus or toward the lumen of the duct (Figs. 2, 3, 4, and 8). Their nuclei were round or oval and larger than those of the cells of the parotid acini or of secretory or intercalated ducts (Figs. 1, 2, 5, and 6). They usually showed a small nucleolus, although occasionally two nucleoli could be seen. The cells increased in size toward the center of the alveolar mass, where they were spherical, polyhedral, or irregular in shape. Their cytoplasm was vacuolated, the vacuoles being larger in the cells more centrally situated or close to the opening of the alveolus into the lumen of the duct (Figs. 1 to 8). Some of the nuclei of these cells were similar to those of the peripheral cells, but others were irregular and pyknotic. In some cells no nuclei could be seen. In many cases the

TABLE II  
*Data on the Cases in Which the Parotid Glands Were the Site of Tumors and in Which Sebaceous Glands Also Were Found*

No.	Sex	Age	Side	Diagnosis of the tumor	Amount of parotid gland available	State of the parotid	Sebaceous glands
1	F	23	?	Mixed tumor	Small piece	Normal	+
2	F	33	?	Mixed tumor	Small piece	Slight atrophy	++
3	?	33	?	Muco-epidermoid tumor	Very small piece	Slight atrophy	+
4	F	60	?	Adenoma	Very small piece	Moderate atrophy	+
5	F	68	?	Mixed tumor	Very small piece	Moderate atrophy	+
6	F	52	Left	Muco-epidermoid tumor	Small piece	Normal	+
7	M	25	?	Mixed tumor	Small piece	Normal	+
8	M	31	Left	Mixed tumor	A piece	Slight atrophy	+
9	M	42	Left	Mixed tumor	Small piece	Moderate atrophy	+
10	M	21	Right	Mixed tumor	Small piece	Slight atrophy	+
11	M	24	Right	Mixed tumor	Very small piece	Slight atrophy	+
12*	M	50	Left	Adenoma	Small piece	Slight atrophy	++
13	F	19	Left	Mixed tumor	Small piece	Slight atrophy	+
14	F	31	Left	Mixed tumor	A piece	Slight atrophy	++
15	F	25	Right	Carcinoma	A piece	Moderate atrophy	++
16	M	5	Left	Carcinoma	Small piece	Slight atrophy	++
17	M	34	Left	Muco-epidermoid tumor	Small piece	Slight atrophy	+
18	M	21	Left	Muco-epidermoid tumor	A piece	Slight atrophy	++
19	F	38	Left	Muco-epidermoid tumor	Small piece	Slight atrophy	++
20	M	36	Left	Carcinoma	Small piece	Slight atrophy	++
21	M	34	Right	Muco-epidermoid tumor	Small piece	Moderate atrophy	+
22	M	57	Right	Mixed tumor	A piece	Slight atrophy	+
23	M	44	Right	Muco-epidermoid tumor	A piece	Moderate atrophy	+
24	F	17	Left	Carcinoma	A piece	Moderate atrophy	+
25	F	34	Left	Carcinoma	A piece	Slight atrophy	+
26	M	28	Right	Mixed tumor	Small piece	Normal	+
27	M	77	Left	Mixed tumor	Small piece	Atrophy	+
28	M	46	Right	Mixed tumor	Small piece	Moderate atrophy	+
29	F	40	Right	Mixed tumor	A piece	Moderate atrophy	++
30	F	47	Right	Mixed tumor	Very small piece	Atrophy	+
31	F	37	Left	Muco-epidermoid tumor	Very small piece	Slight atrophy	++
32	M	57	Right	Carcinoma	Small piece	Moderate atrophy	+
33	F	51	Left	Mixed tumor	A piece	Slight atrophy	+

\* Case from Memorial Hospital, New York City.

large cells with shrunken nuclei were separating into the lumen of the duct, forming a holocrine secretion (Figs. 1, 4, and 7). Mitotic figures were seen only in the cells of the periphery of the alveoli (Fig. 7). The alveoli usually were single at the end of the blind ducts but sometimes two or three alveoli opened into a duct to form a simple branched gland (Fig. 8). In frozen sections, stained with Hortega's silver carbonate, it was seen that the empty vacuoles, observed in the paraffin sections, were filled with a translucent, refringent substance. When these same sections were stained subsequently with scharlach R, the substance contained in the vacuoles varied from orange to red. Sections from paraffin-embedded tissue stained with Mayer's mucicarmin and Best's carmine failed to show mucin or glycogen in the vacuoles. The presence of sebaceous-gland-like structures was demonstrated in frozen sections from only 14 of 22 parotid glands which showed them in the paraffin sections and which were saved in formalin, although hundreds of sections were studied from the remaining 8 cases.

#### COMPARATIVE STUDY OF THE FINDINGS IN BOTH GROUPS

From the microscopic findings, it was evident that the epithelial structures found in the parotid glands had morphologic and tinctorial characteristics similar to those of sebaceous glands, particularly of the kind seen in areas where such glands are not associated with hair. These structures will be designated as sebaceous glands in the discussion which follows.

The findings and certain clinical data for the patients in whom the sebaceous glands were found are summarized in Tables II and III, but some of the facts recorded there should be emphasized.

*Incidence of Sebaceous Glands.* Thirty-three parotid glands of group 1 showed sebaceous glands and 28 in group 2, which represents 24.8 per cent and 28 per cent, respectively. In group 2, sebaceous glands were found in both parotid glands in 11 persons and in one parotid gland only in 6 persons, making a total of 17. In other words, 33 per cent of the persons whose parotid glands were examined at autopsy showed sebaceous glands.

*Incidence in Relation to Sex.* The 33 parotid glands of group 1 that showed sebaceous glands were from 17 males and 15 females, with one person whose sex was not recorded. In group 2, 12 of those in whom sebaceous glands were found were male and 5 female. This apparent preponderance in the male sex is not significant, because 33 persons of this group were male and only 18 female.

*Incidence in Relation to Age.* The occurrence of sebaceous glands

TABLE III  
*Data on the Autopsy Cases in Which the Parotid Glands Showed Sebaceous Glands*

No.	Sex	Age	Cause of death	State of the parotid	Sebaceous gland	Remarks
1*	M	70	Bronchial asthma, retroperitoneal hemorrhage	Moderate atrophy	+	Positive fat stain
2	M	67	Myocardial infarction, squamous cell carcinoma of tongue and floor of mouth	Moderate atrophy	++	Positive fat stain
3	M	54	Hypernephroma of left kidney with multiple metastases, diabetes	Slight atrophy	+	No sebaceous gland found in frozen sections
4*	M	76	Carcinoma of stomach, bronchopneumonia	Marked atrophy	+	No sebaceous gland found in frozen sections
5*	F	21	Spongioblastoma polare, acute purulent lobular pneumonia	Slight atrophy	+	Positive fat stain
6*	M	22	Subdural hematoma, multiple fractures	Moderate atrophy	+	No sebaceous gland found in frozen sections
7*	F	49	Carcinoma of the breast, with multiple metastases	Slight atrophy	++	No sebaceous gland found in frozen sections
8	F	64	Third-degree burns, carcinoma of the thyroid	Slight atrophy	+	No sebaceous gland found in frozen sections
9	M	43	Myelosarcomatosis, bronchopneumonia	Slight atrophy	++	Positive fat stain
10	M	25	Chronic glomerulonephritis, uremia, peptic ulcer	Normal	+	Sebaceous glands negative for glycogen and mucin
11	F	15	Polycythemia, massive infarction of occipital and parietal portion of brain	Slight atrophy	+	Sebaceous glands negative for glycogen and mucin
12	M	13	Medulloblastoma of cerebellum invading meninges and spinal cord	Slight atrophy	+	Positive fat stain
13	F	36	Dicoumarol poisoning	Slight atrophy	+	Positive fat stain
14	M	6	Encephalitis	Normal	++	Positive fat stain
15	M	21	Epidural hemorrhage	Normal	++	Positive fat stain
16	M	19	Bullet wound	Normal	++	Positive fat stain
17*	M	50	Multiple bullet wounds	Normal	+	Positive fat stain

\* Cases in which only one parotid gland showed sebaceous glands.

had no relation to age, as can be seen clearly in Table IV, which shows that the youngest person was 5 years old and the oldest 77 years in group 1, and 6 years and 76 years in group 2. The concentration noted from the second to the sixth decade in group 1 probably cannot be considered significant since that is a period in which most salivary gland tumors occur.

TABLE IV  
*Age Distribution by Decades of Cases with Sebaceous Glands*

Age	Tumor cases* (group 1)	Autopsy cases (group 2)
1-10	1 (Youngest 5 years)	1 (Youngest 6 years)
11-20	2	3
21-30	7	4
31-40	10	1
41-50	5	3
51-60	5	1
61-70	1	3
71-80	1 (Oldest 77)	1 (Oldest 76)

\* Age not known for 1 case.

*Sebaceous Glands and Glandular Atrophy.* There was no association between atrophy of the parotid gland and the occurrence of sebaceous glands since they were found in parotid glands showing all degrees of atrophy or no atrophy at all.

*Number and Degree of Development of the Sebaceous Glands.* The study of the material in relation to frequency and to degree of development showed that sebaceous glands were more numerous in the cases of group 1, in which they also reached a larger size and sometimes presented a branched appearance, while in group 2 they were less numerous, smaller, and only one branched gland was seen (Figs. 14 to 20). The average number of sebaceous glands found in the sections from each case of group 1 was 4.5, while in group 2 it was 2.5. These figures, although significant, do not adequately express the preponderance clearly observed in the study of the material, for it was noticed that there was greater frequency of occurrence of two or more sebaceous glands in one microscopic field in cases from group 1 (Figs. 9 to 13), while in group 2 on only two occasions were two sebaceous glands seen in one field (Fig. 14). This lack of agreement between observation and tabulation can be explained by the fact that the amount of normal parotid gland available for study from each case of group 1 was often one or two small sections, while in cases from group 2 at least 10 sections obtained from two different blocks were studied. In regard to size, the largest sebaceous glands were seen in parotid glands of group 1 in which they reached 350  $\mu$  in diameter.

*Relation of Sebaceous Glands and Type of Tumor.* Sebaceous glands were found in association with 17 mixed tumors, 8 neoplasms of the muco-epidermoid type recently separated from the so-called mixed tumor group,<sup>5</sup> 6 carcinomas, and 2 adenomas. The great frequency with which sebaceous glands were present in parotid glands that were the site of muco-epidermoid tumors should be noticed. This can be brought out better by two facts. First, examples of this type comprised 24 per cent of the tumors associated with sebaceous glands. This figure is very high if one considers that the incidence of the muco-epidermoid tumor in relation to all salivary gland tumors is 5+ per cent.<sup>5</sup> Second, sebaceous glands were found in 8 of 11 cases of muco-epidermoid tumor in which there was normal parotid gland present; or, in other words, they were found in 73 per cent of the parotid glands that were the site of such tumors. The association of sebaceous glands and carcinoma in the same parotid gland also seems to be of interest, because this occurred in 18 per cent of the cases of group 1 in which sebaceous glands were seen. This is a higher incidence than that of carcinoma in relation to mixed tumors, which was estimated to be 14+ per cent in the material studied for this report. This figure comes close to the percentage for malignant tumors of the parotid gland found by Stein and Geschickter,<sup>6</sup> which was 17 per cent, and the 15+ per cent obtained from the cases studied by Benedict and Meigs,<sup>7</sup> who had 30 examples of carcinoma in 203 cases of parotid tumors.

#### COMMENTS

If it be accepted that the epithelial structures found in parotid glands are truly sebaceous glands, it becomes necessary to explain how these accessory skin structures happen to be present in this location. Their occurrence in the mucosa of the mouth, where they have long been recognized and their presence designated as Fordyce's disease, has been explained as resulting from aberrant buds along the fetal line of closure.<sup>8,9</sup> This explanation cannot be accepted for their occurrence in the parotid and submaxillary glands, because there is no line of closure in those glands and because there is definite proof that these sebaceous glands are derived from duct epithelium, which seems to have the ability to give origin to them. This ability probably can best be explained on the basis of a latent potentiality of differentiation in the adult epithelium. The existence of this potentiality is likely because, as Gruenwald<sup>10</sup> stated, "latent developmental potencies and lability of determination and differentiation are not, as early investigators believed, peculiarities of embryonic cells." If this latent potentiality of the duct epithelium is accepted, it would be easy to understand its differentiation into sebaceous



glands since both parotid and sebaceous glands are developed from the ectoderm.<sup>11-13</sup> Whether or not this explanation is accepted, it is evident that the duct epithelium can give origin to sebaceous glands in normal parotid glands as well as in those which are the site of neoplasia. Moreover, the latter group seems to have a greater tendency toward such differentiation, as appears to be substantiated (1) by the occurrence of sebaceous glands in greater numbers and in a more advanced state of development in such parotid glands than in those considered to be normal; (2) by the frequency with which sebaceous glands were seen in parotid glands which had given origin to tumors of the muco-epidermoid type, in which it has been observed that the duct epithelium may undergo transformation into mucus-forming cells and also into cells capable of showing different stages of transformation, varying from the normal type cell of the duct epithelium to cornifying squamous elements; and (3) by the occurrence of sebaceous glands in two parotid glands that were the site of pure adenomas, tumors that in themselves may be considered as the direct result of the latent potentiality of the glandular epithelium to undergo differentiation into cells of a new type.<sup>1</sup> It also appears that the epithelium of the parotid gland seems to be more liable to undergo differentiation than that of the submaxillary gland, as is shown by the greater incidence of sebaceous glands in the former. This is further proved by the fact that Hamperl<sup>2</sup> found only 4 instances of sebaceous-gland-like transformation in submaxillary glands in a study of salivary glands in 85 persons, while in the material of the present report this was observed in 28 parotid glands obtained from 51 individuals. From what has been said, it seems logical to think that an epithelium, in which an exaggerated latent potentiality of differentiation exists, is prone to give origin not only to normal structures, but also to tumors in which the cell component may resemble various epithelial elements of ectodermal origin, such as those sometimes found in salivary gland tumors. Thereby are explained some findings which have been noticed repeatedly in the mixed tumors of the salivary glands, such as the presence of squamous epithelium<sup>14-17</sup> and keratohyalin, the resemblance of some salivary gland tumors to the basal cell carcinoma of the skin,<sup>18-20</sup> to the adamantinomas,<sup>20-22</sup> and also to some tumors occurring in relation to the skin but with characteristics similar to mixed salivary gland tumors.<sup>23</sup>

#### SUMMARY

Sections from 100 normal parotid glands and from 133 parotid glands which were the site of tumors were studied to find out (1) if structures resembling sebaceous gland are present in normal parotid glands, (2) if

such structures are present in parotid glands that are the site of tumor, and (3) if the presence of sebaceous glands might have some significance in the explanation of tumors occurring in the salivary glands.

From this study, the following results were obtained. Structures which could not be differentiated from sebaceous glands, measuring from 50 to 350  $\mu$  in diameter, were seen to originate from intercalated and striated ducts which ended blindly. Such sebaceous glands were present in 28 per cent of the normal parotid glands and in 24.8 per cent of the parotid glands in which tumors had occurred. Their occurrence was not related to sex, age, or state of atrophy of the parotid gland. Sebaceous glands were more numerous and in a more advanced state of development in the parotid glands in which tumors had occurred.

Sebaceous glands were associated with 17 mixed tumors, 8 muco-epidermoid tumors, 6 carcinomas, and 2 adenomas. There appears to be a high incidence of sebaceous glands in parotid glands in which muco-epidermoid tumors, carcinomas, and adenomas develop. There seems to be some evidence of greater susceptibility of the parotid epithelium to undergo differentiation as compared with that of the other salivary glands, which gives a possible explanation for the greater frequency of tumors in the parotid glands.

It is reasonable to believe that the sebaceous glands occurring in the submaxillary and parotid salivary glands arise from duct epithelium owing to the presence of latent potentiality of differentiation in that epithelium. This aids in developing a possible explanation for the origin of some of the components of the mixed tumors.

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[ Illustrations follow ]

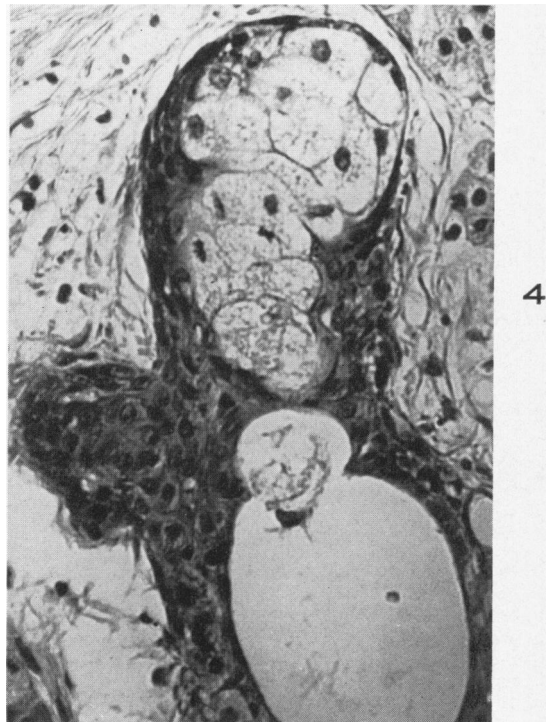
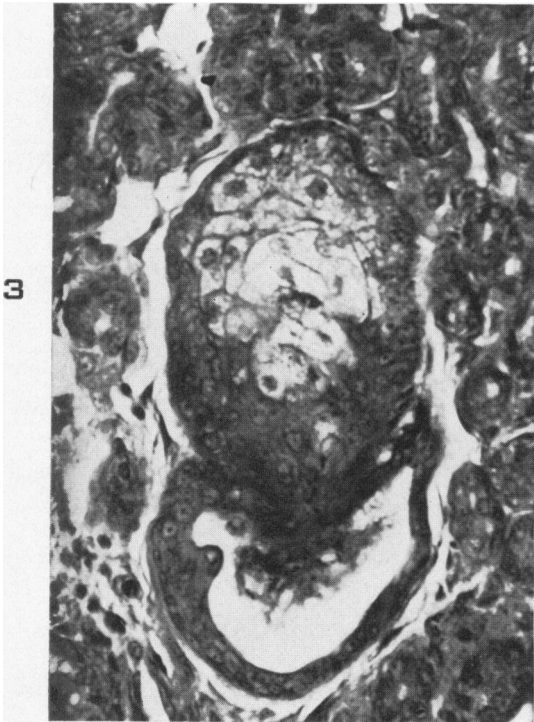
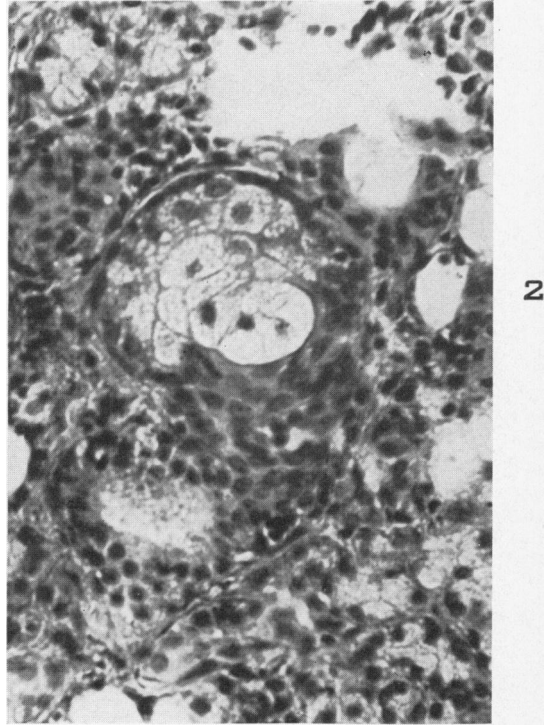
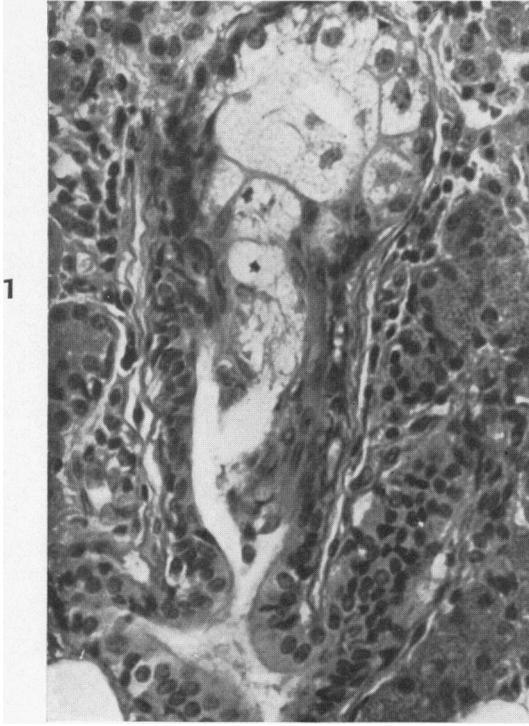
## DESCRIPTION OF PLATES

All photomicrographs were obtained from slides stained with hematoxylin and eosin, unless otherwise stated.

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### PLATE 96

- FIG. 1. Case 18 of Table II. Sebaceous gland arising in a branch of a striated duct. Of note is the holocrine secretion falling into the lumen of the duct.  $\times 375$ .
- FIG. 2. Sebaceous gland in the parotid gland of the oldest person from group 1, case 27 of Table II.  $\times 375$ .
- FIG. 3. Sebaceous gland in the youngest individual of group 1, case 16 of Table II.  $\times 375$ .
- FIG. 4. Sebaceous gland in one of the cases of adenoma of the parotid gland (case 12 of Table II). Of note is the holocrine secretion in the lumen of the duct.  $\times 375$ .

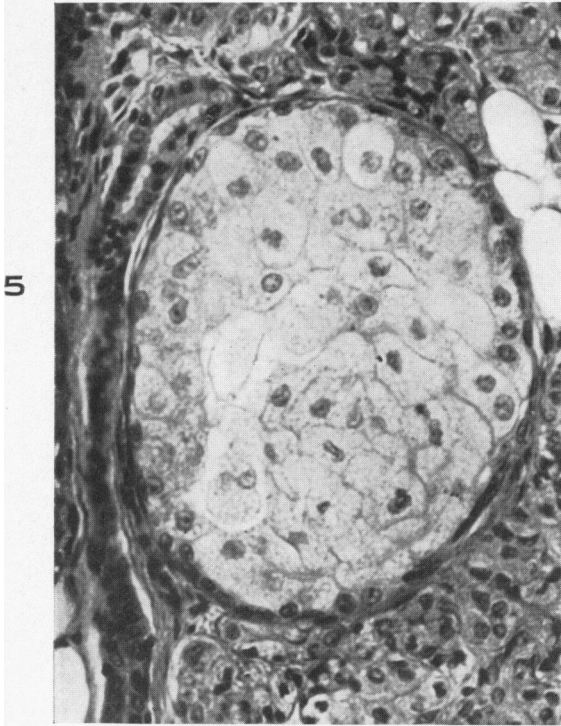


Meza-Chávez

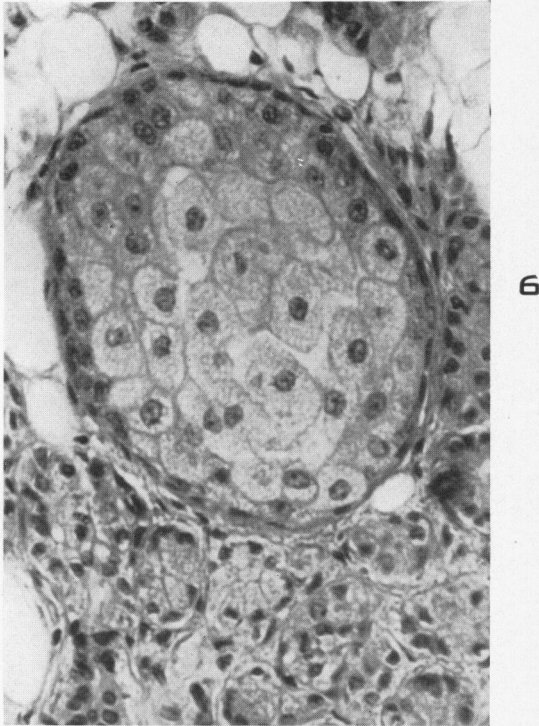
Sebaceous Glands in Parotid Glands

PLATE 97

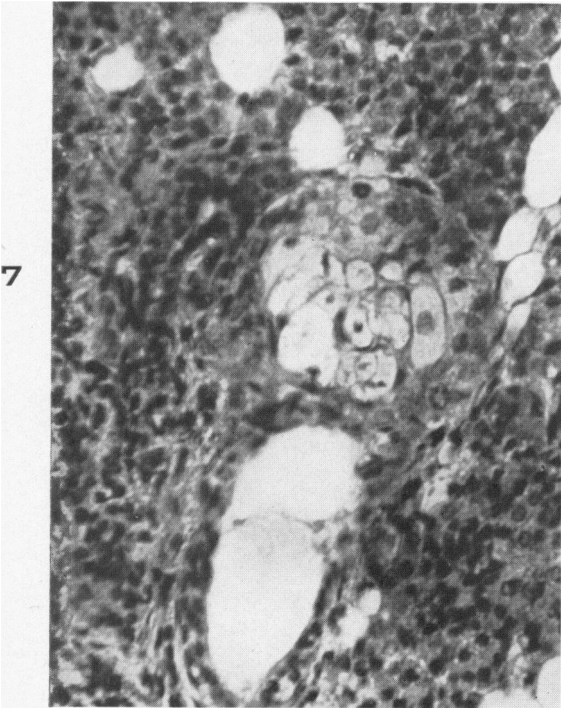
- FIGS. 5 and 6. Sebaceous glands in a normal parotid gland (case 12 of Table III). Of note is the larger size of the nuclei of the sebaceous glands in comparison to the acinar and ductal cells.  $\times 375$ .
- FIG. 7. Sebaceous gland from another normal parotid gland (case 9 of Table III). There is a mitotic figure in a cell at the periphery of the alveolus.  $\times 375$ .
- FIG. 8. Simple branched sebaceous gland from a case of parotid adenoma, case 12 of Table III.  $\times 375$ .



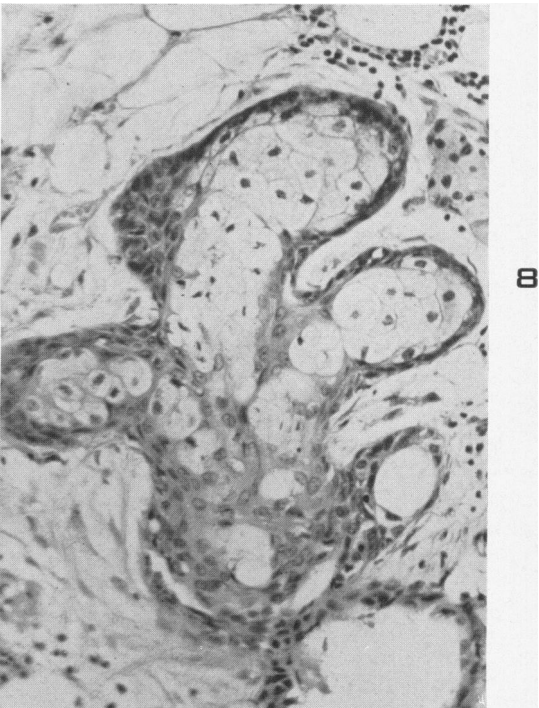
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Sebaceous Glands in Parotid Glands

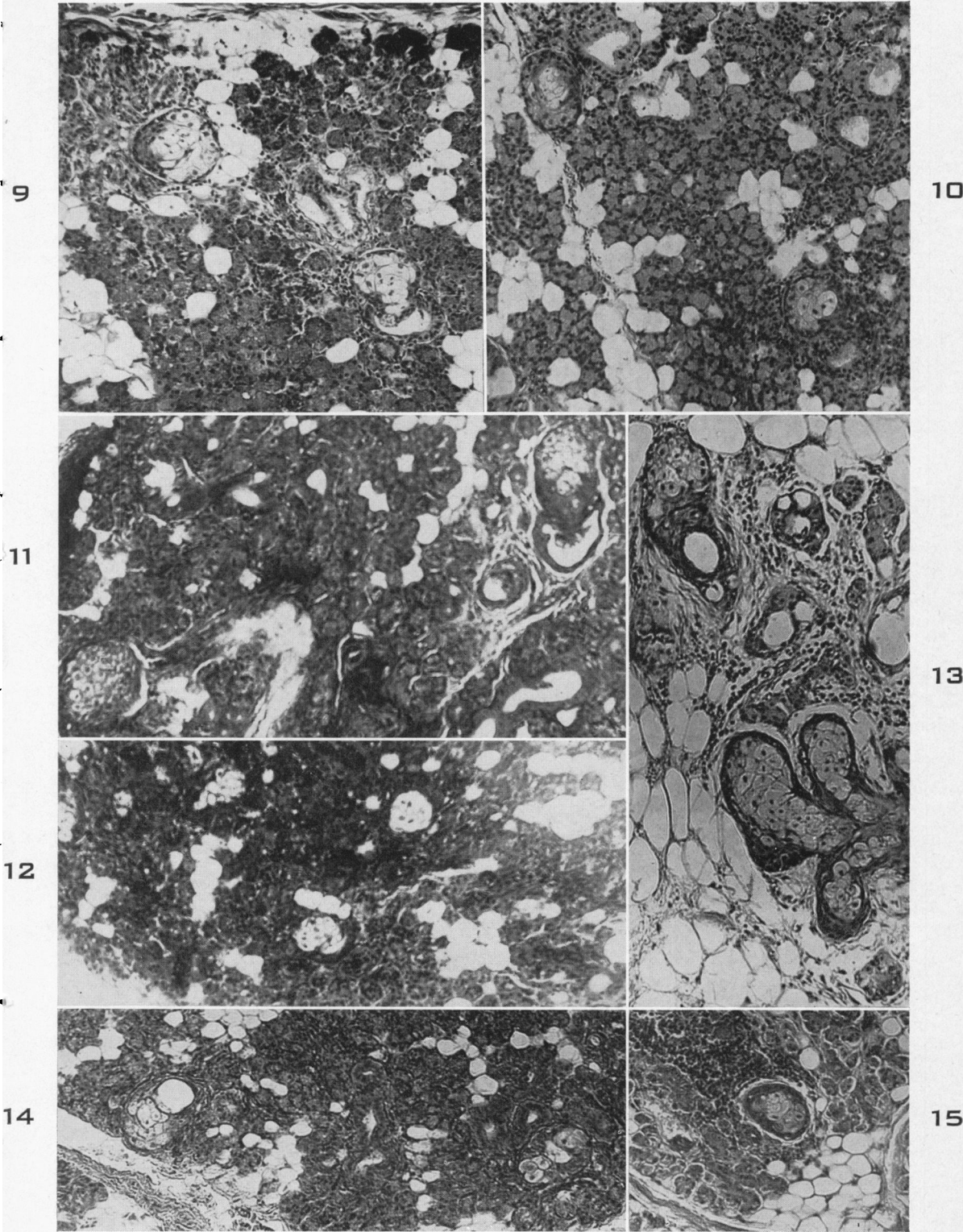
PLATE 98

FIGS. 9 to 13. Parotid glands from group 1 in which two or more sebaceous glands were seen in a single microscopic field (cases 18, 27, 16, 17, and 12, respectively, of Table II).  $\times 115$ .

FIG. 14. Parotid gland from group 2 in which two sebaceous glands are seen in one microscopic field (case 7 of Table III).  $\times 115$ .

FIG. 15. Early development of sebaceous glands in a normal parotid gland (case 13 of Table III).  $\times 115$ .





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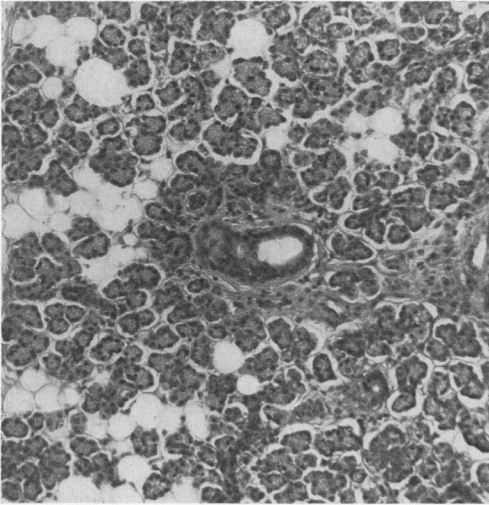
PLATE 99

FIGS. 16 to 18. Three sections from a sebaceous gland arising from an intercalated duct which ends blindly (case 10 of Table III).  $\times 115$ .

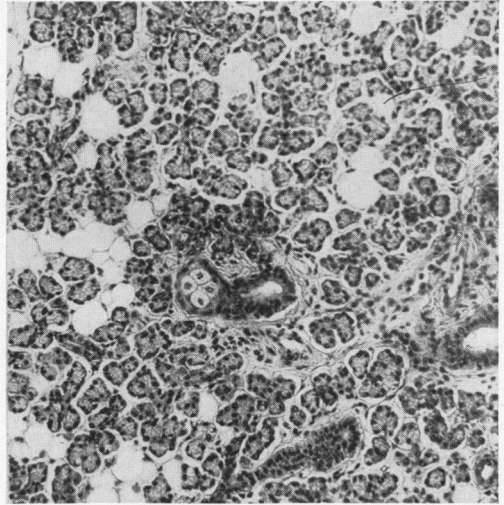
FIGS. 19 and 20. Sebaceous glands from normal parotid glands, with lymphocytic infiltration around them (cases 13 and 15 of Table III).  $\times 115$ .

FIG. 21. Frozen section from a normal parotid gland showing a sebaceous gland (case 9 of Table III). Hortega's silver impregnation and scharlach R stains.  $\times 115$ .

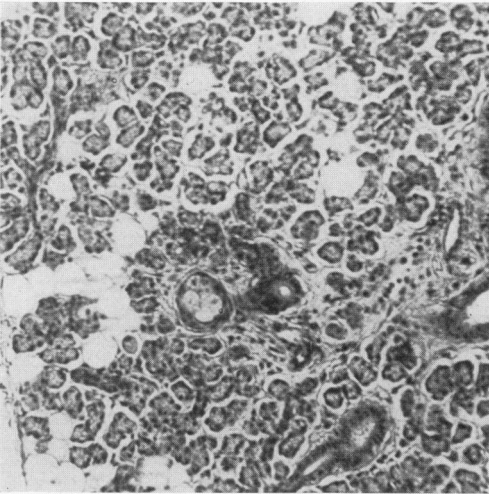
16



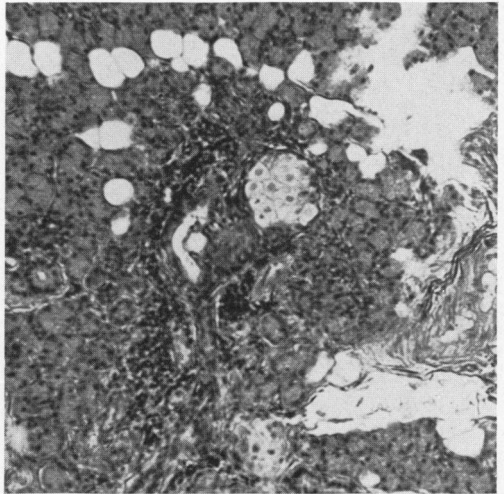
17



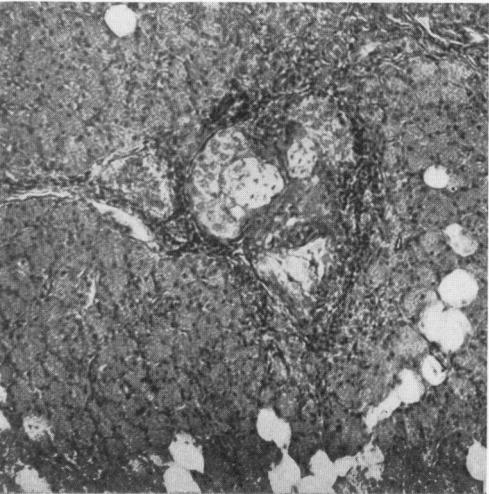
18



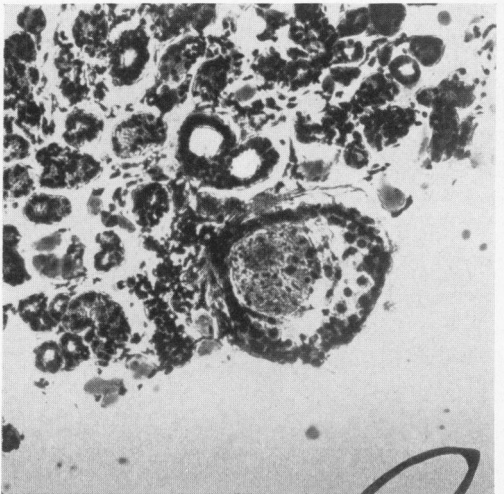
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