CHEMODECTOMAS OCCURRING CONCURRENTLY IN THE NECK (CAROTID BODY), TEMPORAL BONE (GLOMUS JUGULARE) AND RETROPERITONEUM

Report of a Case with Histochemical Observations*

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Rare, solitary carotid body tumors of the neck have long been recognized and their characteristic histologic features described.[1-3] More recently, multiple tumors of similar architecture, occurring in sites distant from the neck, have been studied. Rosenwasser[4] reported the first glomus jugulare tumor, and Kipkie,[5] the first concurrence of carotid body and glomus jugulare tumors. Cragg[6] recorded a case of concurrent tumors of the carotid body and both organs of Zuckerkandl, and Goodof and Lischer[7] described a case in which a carotid body tumor was associated with a microscopically similar neoplasm in the pancreas. Tumors of this type have now been reported from such sites as the middle ear, the nodose ganglion, the aortic and carotid bodies, the orbit,[8] the pancreas and the organs of Zuckerkandl. To avoid use of terminology suggesting sympathetic origin or specific sites of occurrence, the term "chemodectoma" used by Mulligan[9] seems preferable as a general term to include multicentric tumors microscopically resembling the carotid body tumor. Although this term leaves much to be desired, it does emphasize the physiologic role of the parent tissue without implying a specific site or embryologic origin. The present report describes a case in which four chemodectomas, including two in the retroperitoneal region were found at necropsy.

Case Report

In 1935 at 20 years of age, the patient was examined in the Massachusetts Eye and Ear Infirmary because of deafness in the left ear, hoarseness, and difficulty in breathing through the left nostril. Examination showed firm swelling of the lateral pharyngeal and nasopharyngeal walls extending to the choana. Three biopsy specimens revealed "chronic inflammation," and a fourth showed "cavernous hemangioma." In April, 1936, the left carotid artery was ligated at the level of the thyroid cartilage. Two days later the left pharyngeal wall was explored, and a highly vascular fibrous mass was excised.

The patient remained well for 5 years and returned to the hospital

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because of a nontender swelling in the right side of the neck which had been present for one year. Roentgenograms showed marked right retropharyngeal and lateral pharyngeal swelling with displacement of the hyoid bone and larynx to the left. A lymph node removed from the right side of the neck above the carotid bifurcation, revealed "lymphoid hyperplasia." A short course of x-irradiation was given.

He re-entered the Massachusetts General Hospital in November, 1956, complaining of persistent hoarseness due to left vocal cord paralysis, a dry cough, deafness of the left ear, and moderate difficulty in swallowing solids. The left auditory canal contained a mass of foul-smelling granulation tissue. A firm mass, involving the left side of the palate, obstructed the eustachian tube, and a swelling of the right pharyngeal wall extended into the pyriform sinus, producing deviation of the larynx to the left. The base of the tongue was fixed on the left, and both vocal cords were immobile. A large, nontender, nonpulsatile, firm mass was present in the right side of the neck, extending above the mandible and protruding into the pharynx.

Roentgenographic examination of the skull disclosed destruction of the left middle fossa, the left petrous apex and part of the labyrinth. A barium swallow showed the valleculae and the pyriform sinus to be displaced to the left but not invaded.

Exploration of the right neck revealed, at the carotid bifurcation, a well encapsulated purplish tumor which bled profusely. For this reason, no attempt was made to remove it. Two days later, a mass of hemorrhagic soft blue tissue was removed from the left external auditory canal; microscopically this resembled a glomus jugulare tumor.

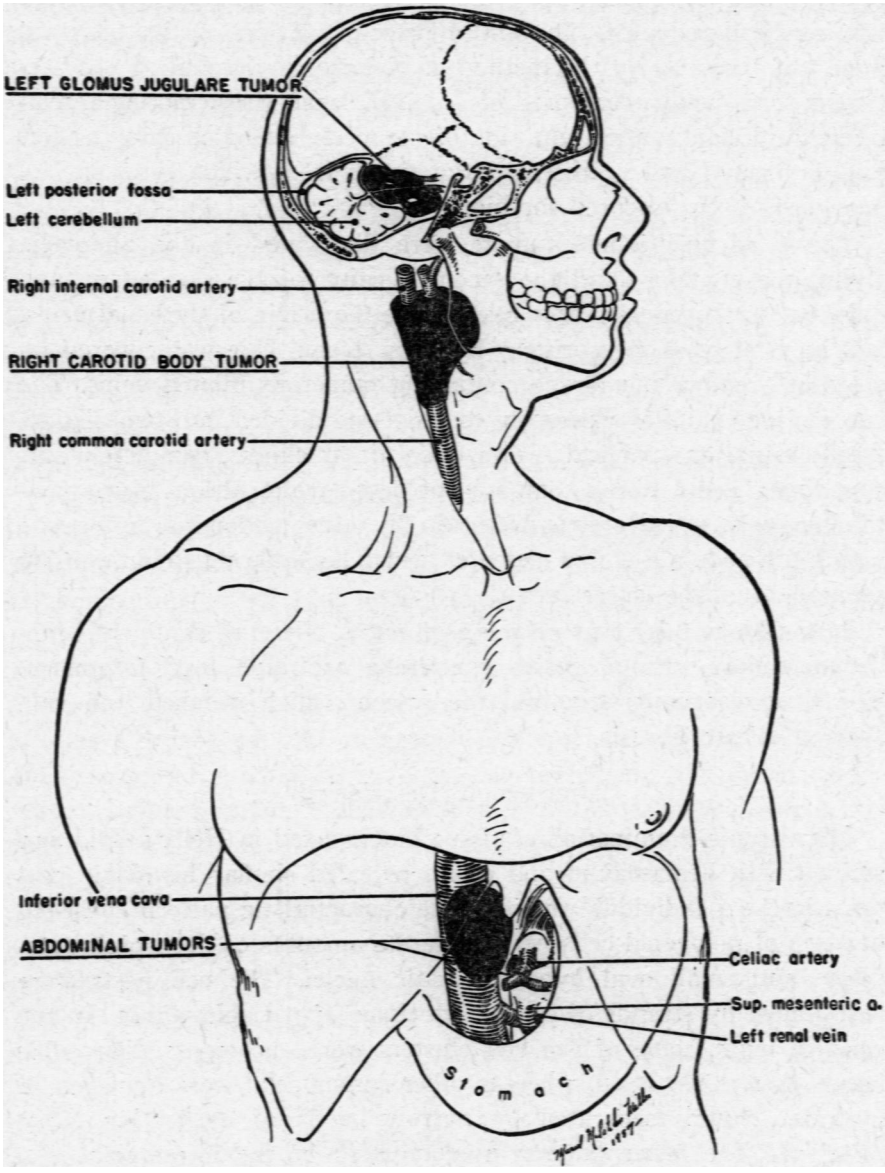
The patient had been examined several times during the preceding 3 years because of weakness and anemia. Examination of the blood showed 8.4 to 10.4 gm. of hemoglobin per hundred cc., normal differential blood counts and a few bizarre red cells in the smear. There was mild erythroid hyperplasia of the marrow. On one occasion, the urine urobilinogen was increased. A diagnosis of low-grade hemolytic anemia was made, and Meticorten therapy was begun. The patient died of bronchopneumonia in December, 1956.

Pathologic Observations

Four distinct tumors of similar gross and microscopic appearance were found at necropsy (Text-figure 1).

A tumor measuring 8 by 6.5 by 1.5 cm. was present in the right side of the neck and extended upward into the floor of the mouth and downward along the course of the common carotid artery. The carotid bifurcation and a segment of the common carotid artery were

embedded within the tumor. The cut surface of the mass revealed slightly lobulated, extremely tough, pink-tan homogeneous tissue (Fig.



Text-figure 1. Drawing indicating the sites of multicentric chemodectomas.

1), which was firmly adherent to the walls of the carotid arteries and to the subcutaneous tissue beneath the mandible. Multiple lymph nodes, including two large nodes from the left neck, were free of neoplasm. The left carotid artery, which had been ligated previously, was represented by a thin fibrous cord.

When the brain was removed, a large, smooth-surfaced, dull pink oval mass, measuring 6 cm. in diameter, projected from the left petrous pyramid and encroached upon the left cerebellar hemisphere and the left cerebral peduncle. The entire petrous portion of the temporal bone was removed by the method of Kelemen,[10] decalcified and sectioned. This tumor, composed of tough pink-tan tissue closely resembling the lesion in the right side of the neck, extended into the left auditory canal and represented the tissue from which sections had previously been procured for biopsy.

The third and fourth tumors were discovered in the abdomen. Lying above and behind the second portion of the duodenum, and adherent to the inferior vena cava above the origin of the renal veins, was an oval mass measuring 7 by 6 by 4 cm. This was covered by a smooth red-tan membrane containing numerous dilated veins. The cut surface exhibited extremely tough tissue divided into two distinct areas: a pink-tan cortical region, 1 cm. in thickness, completely surrounding a central area composed of dense white fibrous tissue containing flecks of calcareous material. The other abdominal lesion was a pink-tan nodule, 1 cm. in diameter, which lay adjacent to but entirely separate from the larger tumor.

In the lungs there was evidence of acute, bilateral, confluent bronchopneumonia with abscesses containing aspirated food fragments. The liver was congested, and the spleen, which weighed 390 gm., showed diffuse fibrosis.

Microscopic Description

Microscopic examination of tissue blocks fixed in Helly's fluid and stained with hematoxylin and eosin, revealed similar histologic patterns in the 4 individual tumors. The characteristic pattern consisted of nests of polygonal cells with moderate amounts of deep pink cytoplasm and small oval hyperchromatic nuclei. The cell nests were surrounded by strands of connective tissue of variable width. In the cervical mass, some of the cell clusters were encompassed by wide bands of fibrous tissue, whereas other tumor cells were arranged in irregular clumps separated by narrow bands of connective tissue (Fig. 3). The latter pattern predominated in the intracranial and small abdominal tumors (Figs. 2 and 7). In sections from the dense central area of the larger abdominal mass, wide sheets of dense fibrous tissue were seen; in this a few clusters of neoplastic cells were embedded (Fig. 5).

Occasional clumps of yellow-brown pigment were scattered in the fibrous tissue in all the tumors. These gave a positive reaction for

iron. Moderate-sized nerve fibers were present in the capsules of the cervical lesion and the larger abdominal mass. Sections from all the tumors stained for reticulum fibers showed strands of delicate fibrils surrounding the clusters of neoplastic cells (Figs. 4, 6 and 8).

Histochemical Observations

Several histochemical procedures for the detection of enzymes, carbohydrates, and lipids were performed on sections of the tumor tissue.

Fresh frozen sections stained for esterase activity by the method of Ravin, Zacks and Seligman[11] revealed moderate cytoplasmic total esterase activity (Fig. 9). After physostigmine inhibition, marked suppression of staining occurred, indicating the presence of significant cholinesterase activity. No attempt was made to distinguish serum cholinesterase from acetylcholinesterase. Fresh frozen and formalin-fixed sections stained for alkaline phosphatase by the Gomori method[12] disclosed no enzymatic activity in the tumor cells. Endothelial cells in the stroma, however, were stained.

Formalin-fixed sections embedded in paraffin and stained by the periodic acid-Schiff method of McManus[13] exhibited rare cells with intracytoplasmic PAS-positive, diastase-resistant granules. These were believed to be macrophages. The cytoplasm of the neoplastic cells was not stained. Formalin-fixed, frozen sections stained for neutral fat with Sudan III showed occasional small intracytoplasmic fat droplets in the tumor cells and larger droplets in scattered stromal macrophages.

By means of the Baker[14] procedure for determining phospholipids, the cytoplasm of the tumor cells was seen to contain minute, deep blue-gray granules (Fig. 10). Control sections cut from blocks which had previously been extracted with hot pyridine revealed a few small gray-black cytoplasmic granules in many tumor cells. No metachromasia appeared in frozen sections stained with toluidine blue. In sections prepared by the chromate and iodate methods of Hillarp and Hökfelt[15] no chromaffin granules were observed. The adrenochrome method of Sevki[16] was negative.

Blocks of frozen tissue from both the cervical and the abdominal neoplasms were extracted and tested for the presence of epinephrine and norepinephrine* by the fluorometric method of Sobel and Henry.[17] Neither mass contained epinephrine. Both contained very small amounts of norepinephrine (0.5 μg. per gm.).

* Grateful acknowledgment is due to Dr. Charles DuToit in whose laboratory the epinephrine and norepinephrine assays on the tumors were performed and to Dr. Philip M. LeCompte who reviewed the slides.

Discussion

As stated in the introduction, neoplasms resembling the carotid body tumor have been found in sites unrelated to the carotid and aortic bodies. Instances of lesions resembling carotid body tumors microscopically have now been reported arising in the glomus jugulare, orbit, pancreas, and organs of Zuckerkandl. The present case illustrates multiple tumors including two which were retroperitoneal.

The occurrence of multiple similar neoplasms[3,5,7,8] raises the possibility of metastases from malignant carotid body tumors. The lesions found in the present case, however, showed no evidence of malignancy or invasion of surrounding structures upon microscopic examination. Only a few acceptable examples of metastases to mediastinal lymph nodes, lung and bone are recorded in this type of neoplasm.[18] A diagnosis of malignancy determined on the basis of the microscopic characteristics of a primary tumor, in the absence of demonstrable metastasis, must be considered inconclusive.[19] It is believed, therefore, that chemodectomas arise independently in multiple foci.[5,7,8,20]

The derivation of carotid body tissue has been the subject of considerable discussion for many years. The acceptance earlier by Kohn[23,24] of the sympathetic origin of this tissue has been questioned by Hollinshead.[25] The current evidence provided by Heymans and Bouckaert,[26] Schmidt and Comroe[27] and others, suggests that the carotid body is a chemoceptor and not a gland of internal secretion. The hypothesis of origin from sympathetic nerve tissue is based primarily on incompletely established embryologic evidence and also on the occasional reports of positive chromaffin reaction in carotid body tumors.

Attempts to demonstrate a chromaffin reaction by several methods in the present case all failed. However, even if found, the chromaffin reaction is inadequate evidence to indicate the presence of epinephrine. Modern views of the chromaffin reaction[15,28] indicate that epinephrine is oxidized to adrenochrome and then polymerized to form brown pigment in the presence of oxidants such as dichromate or periodate. This reaction occurs with polyphenols, aminophenols and ortho- and para-polyamines and therefore is not specific for epinephrine.

Epinephrine could not be demonstrated by a chemical method in the case reported by Cragg,[6] and two bioassays of carotid body tumors by LeCompte[20] revealed negligible vasopressor activity in one case and moderate activity in the second. The chemical nature of the substance responsible for vasopressor activity was not determined. In the present case, a sensitive fluorometric method[17] failed to dis-

close epinephrine in either the neck or the abdominal lesions. A small amount of norepinephrine, probably associated with nerve endings, was found. The lack of specific chemical identification of epinephrine in any of the recorded carotid body tumors indicates that chemodectomas lack epinephrine and are not clearly of sympathetic origin. For these reasons, the term "chemodectoma"[9] seems preferable to "nonchromaffin paraganglioma" or "carotid body tumor" for tumors arising in sites other than the carotid or aortic bodies, even though these other sites have not been proved to contain functioning chemoceptor tissue. The fortuitous occurrence of abdominal chemodectomas may indicate the presence of chemoceptor tissue in sites not previously recognized as part of the chemoceptor system.

The histochemical detection of cholinesterase activity in the cells of a chemodectoma is of interest although it fails to shed light on the origin of these cells. By chemical means, Hollinshead and Sawyer[29] demonstrated small amounts of acetylcholinesterase and serum cholinesterase in the carotid body cells of the cat. The serum type cholinesterase was demonstrated histochemically in the carotid body of the cat by Koelle.[30] These observations fail to exclude or confirm a sympathetic origin of this tissue, because adrenal medulla and sympathetic ganglia also contain cholinesterase.[29,31]

Another previously undescribed observation made in the present histochemical survey, was the finding of variable numbers of phospholipid granules in the cytoplasm of the tumor cells. Granular cytoplasm in carotid body tumor cells has been noted frequently.[20] LeCompte attributed the existence of variable granularity in part to technical manipulation. However, de Castro[32] believed that apparent chromaffin reactions in the carotid body were due to granular lipoid substances in the cells. Hollinshead[25] confirmed the presence of cytoplasmic granules; however, he believed they were not lipids but might be mitochondria. More recent studies have indicated that mitochondria are rich in phospholipid,[33] and therefore the phospholipid granules demonstrated by the Baker method may well be mitochondria.

Summary

A 41-year-old man was found to have 4 chemodectomas, one in the right carotid body, one in the left glomus jugulare, and two in the retroperitoneal region. The probable origin of chemodectomas in other sites than the neck suggests the possibility of normally occurring chemoceptor tissue not previously recognized in these areas.

The origin of these tumors from other than sympathetic tissue is suggested by the absence of epinephrine.

Histochemical tests revealed the presence of cholinesterase, phospholipid and small amounts of neutral fat but no glycogen in the cytoplasm of the neoplastic cells.

REFERENCES

1. Kopfstein, W. Beitrag zur Kenntniss der Geschwülste der Carotisdrüse. *Wien klin. Rundschau*, 1895, 9, 83–85; 97–99; 117–118.
2. Bevan, A. D., and McCarthy, E. R. Tumors of the carotid body. *Surg., Gynec. & Obst.*, 1929, 49, 764–779.
3. Rankin, F. W., and Wellbrock, W. L. A. Tumors of the carotid body. Report of twelve cases including one of bilateral tumor. *Ann. Surg.*, 1931, 93, 801–810.
4. Rosenwasser, H. Carotid body tumor of the middle ear and mastoid. *Arch. Otolaryng.*, 1945, 41, 64–67.
5. Kipkie, G. F. Simultaneous chromaffin tumors of the carotid body and the glomus jugularis. *Arch. Path.*, 1947, 44, 113–118.
6. Cragg, R. W. Concurrent tumors of the left carotid body and both Zuckerkandl bodies. *Arch. Path.*, 1934, 18, 635–645.
7. Goodof, I. I., and Lischer, C. E. Tumor of the carotid body and the pancreas. *Arch. Path.*, 1943, 35, 906–911.
8. Lattes, R. Nonchromaffin paraganglioma of ganglion nodosum, carotid body and aortic-arch bodies. *Cancer*, 1950, 3, 667–694.
9. Mulligan, R. M. Chemodectoma in the dog. (Abstract) *Am. J. Path.*, 1950, 26, 680.
10. Kelemen, G. Removal of the petrous bone from the cranial base for macro- and microscopic investigation. *Ann. Otol. Rhin. & Laryng.*, 1952, 61, 457–464.
11. Ravin, H. A.; Zacks, S. I., and Seligman, A. M. The histochemical localization of acetylcholinesterase in nervous tissue. *J. Pharmacol. & Exper. Therap.*, 1953, 107, 37–53.
12. Gomori, G. Microtechnical demonstration of phosphatase in tissue sections. *Proc. Soc. Exper. Biol. & Med.*, 1939, 42, 23–26.
13. McManus, J. F. A. Histological demonstration of mucin after periodic acid. *Nature, London*, 1946, 158, 202.
14. Baker, J. R. The histochemical recognition of lipine. *Quart. J. Micr. Sci.*, 1946, 87, 441–470.
15. Hillarp, N., and Hökfelt, B. Histochemical demonstration of noradrenaline and adrenaline in the adrenal medulla. *J. Histochem.*, 1955, 3, 1–5.
16. Pearse, A. G. E. Histochemistry, Theoretical and Applied. Little Brown & Co., Boston, 1954, p. 476.
17. Sobel, C., and Henry, R. J. Determination of catecholamines (adrenalin and noradrenalin) in urine and tissue. *Techn. Bull. Reg. M. Technol.*, 1957, 27, 18–23.
18. Goormaghtigh, N., and Pattyn, S. A presumably benign tumor and a proved malignant tumor of the carotid body. *Am. J. Path.*, 1954, 30, 679–693.
19. Harrington, S. W.; Clagett, O. T., and Dockerty, M. B. Tumors of the carotid body. *Ann. Surg.*, 1941, 114, 820–833.
20. LeCompte, P. M. Tumors of the carotid body. *Am. J. Path.*, 1948, 24, 305–321.

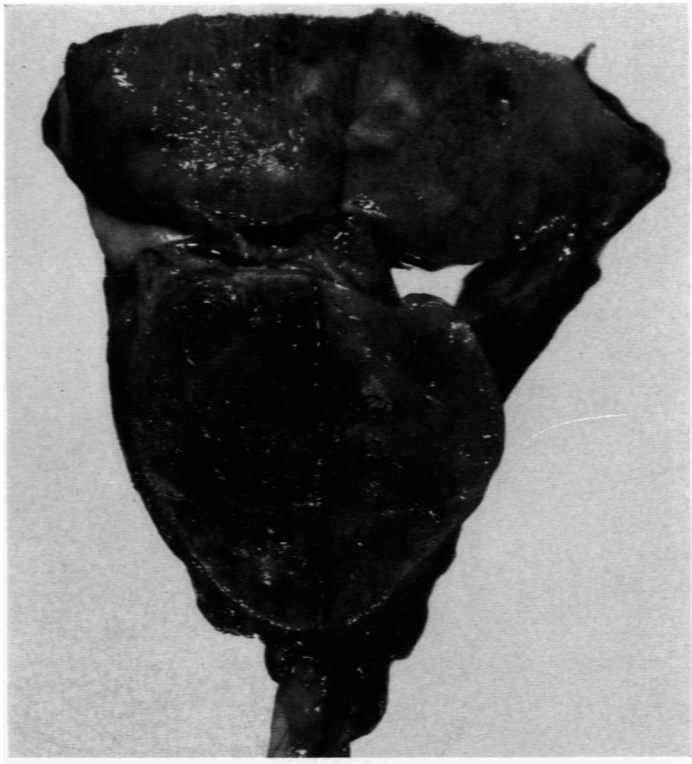
21. Smith, C. The origin and development of the carotid body. *Am. J. Anat.*, 1924–1925, **34**, 87–131.
22. Boyd, J. D. The development of the human carotid body. *Contrib. Embryol.*, 1937, **26**, 3–31.
23. Kohn, A. Ueber den Bau und die Entwicklung der sog. Carotisdrüse. *Arch. mikr. Anat.*, 1900, **56**, 81–148.
24. Kohn, A. Das chromaffine Gewebe. *Erg. Anat.*, 1902, **12**, 253–348.
25. Hollinshead, W. H. A cytological study of the carotid body of the cat. *Am. J. Anat.*, 1943, **73**, 185–213.
26. Heymans, C., and Bouckaert, J. J. Les Chémo-récepteurs du sinus carotidien. *Ergebn. d. Physiol.*, 1939, **41**, 28–55.
27. Schmidt, C. F., and Comroe, J. H., Jr. Functions of the carotid and aortic bodies. *Physiol. Rev.*, 1940, **20**, 115–157.
28. Richter, D., and Blaschko, H. An oxidation product of adrenaline. *J. Chem. Soc., London*, 1937, 601–606.
29. Hollinshead, W. H., and Sawyer, C. H. Mechanisms of carotid body stimulation. *Am. J. Physiol.*, 1945, **144**, 79–86.
30. Koelle, G. B. The elimination of enzymatic diffusion artifacts in the histochemical localization of cholinesterases and a survey of their cellular distributions. *J. Pharmacol. & Exper. Therap.*, 1951, **103**, 153–171.
31. Hagen, P. The distribution of cholinesterase in the chromaffine cell. *J. Physiol.*, 1955, **129**, 50–52.
32. DeCastro, F. Sur la structure et l'innervation du sinus carotidien de l'homme et des mammifères. Nouveaux faits sur l'innervation et la fonction du glomus caroticum. *Travaux de lab. de recherches biol. de l'Univ. de Madrid*, 1927–1928, **25**, 331–380.
33. Lindberg, O., and Ernster, L. Chemistry and Physiology of Mitochondria and Microsomes. In: Protoplasmatologia Handbuch der Protoplasmaforschung, Heilbrunn, L. V., and Weber, F. (eds.). Springer-Verlag, Wien, 1954, Band III, pp. 1–136.

[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Gross appearance of carotid body tumor.

FIG. 2. Microscopic appearance of tumor projecting from temporal bone. Hematoxylin and eosin stain. × 150.



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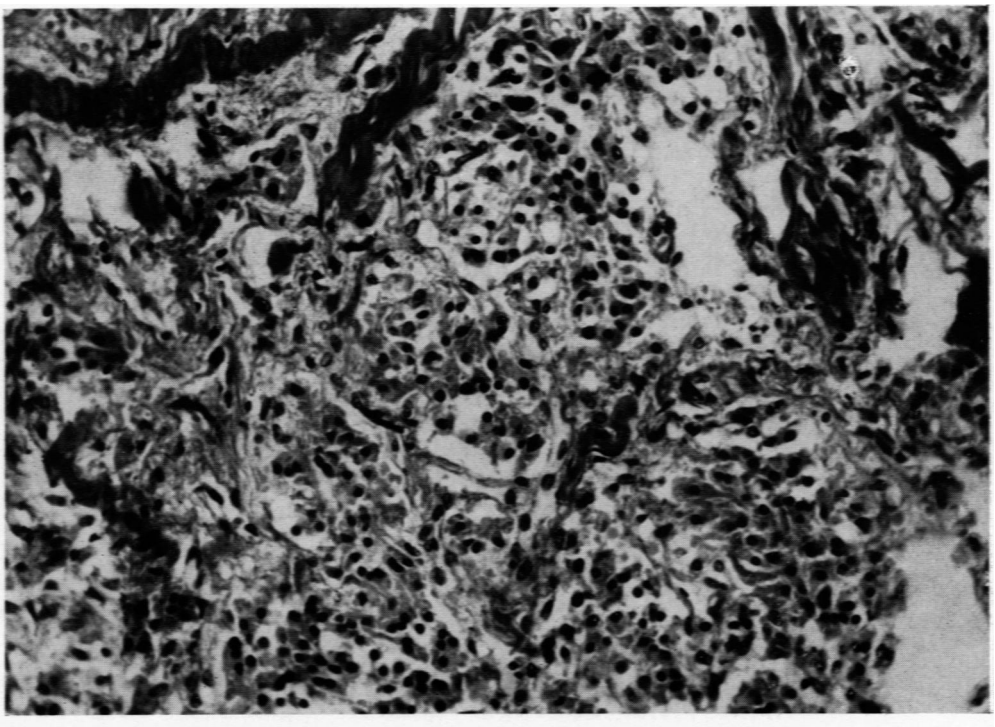

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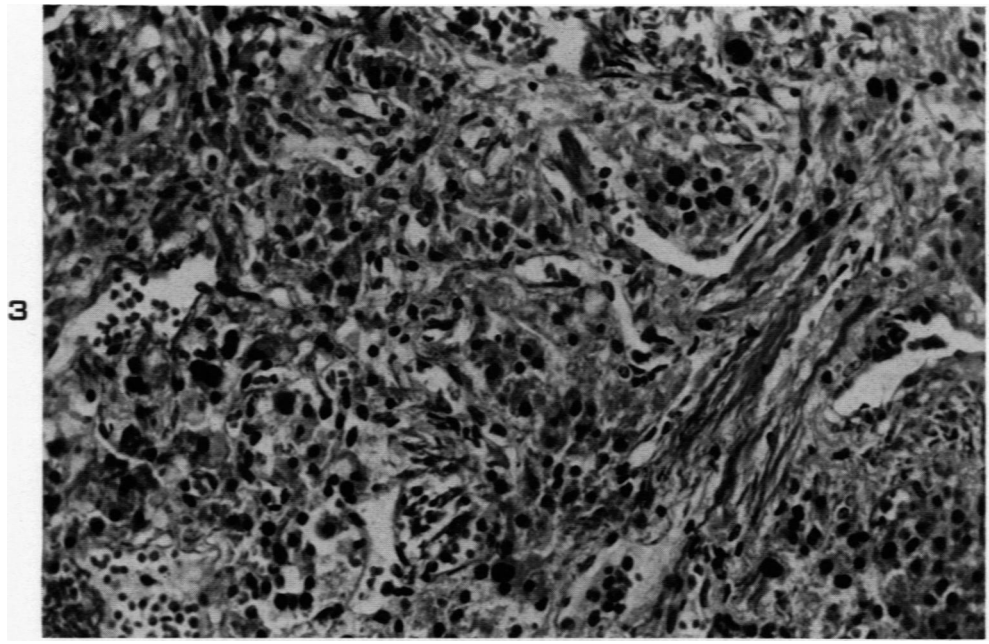


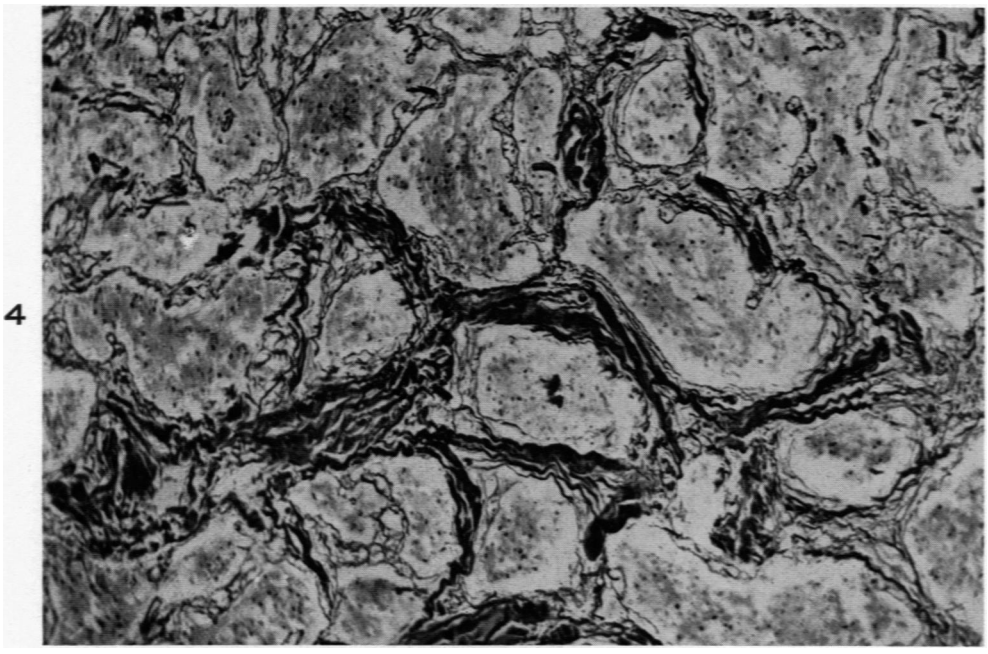
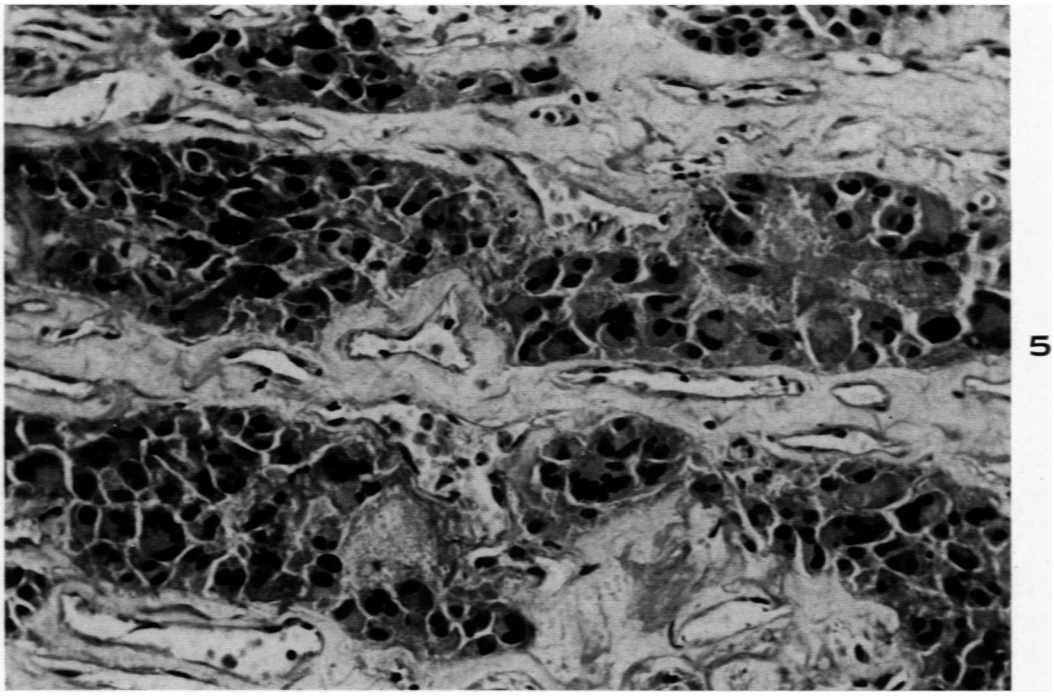


FIG. 3. Microscopic appearance of carotid body tumor. Hematoxylin and eosin stain. × 200.

FIG. 4. Carotid body tumor, showing cell clusters surrounded by dark-staining fibrils. Reticulum stain. × 200.



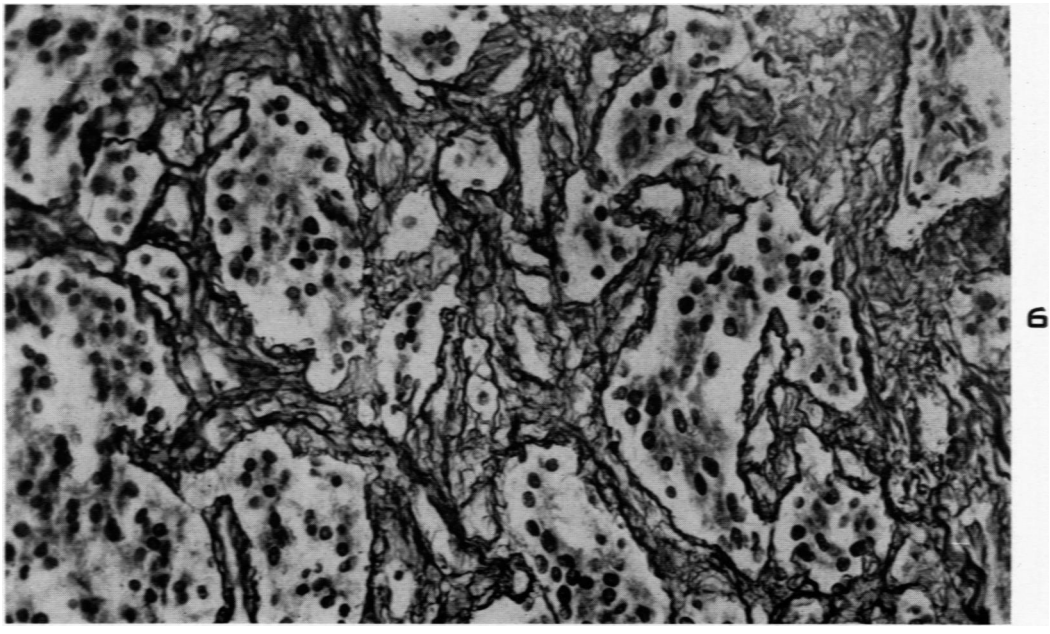
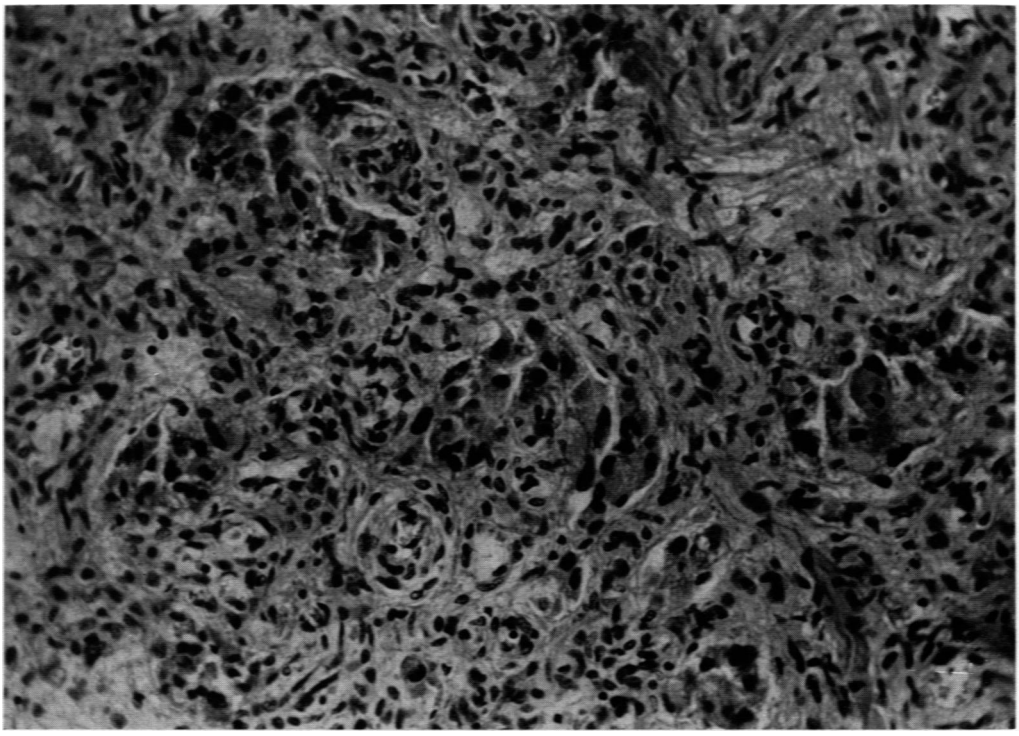


FIG. 5. Microscopic appearance of larger abdominal lesion showing cell clusters and surrounding fibrous tissue. Hematoxylin and eosin stain. × 300.

FIG. 6. Large abdominal tumor, showing cell clusters. Reticulum stain. × 200.

FIG. 7. Microscopic appearance of smaller abdominal mass. Hematoxylin and eosin stain. × 300.

FIG. 8. Smaller abdominal tumor, showing cell clusters. Reticulum stain. × 200.



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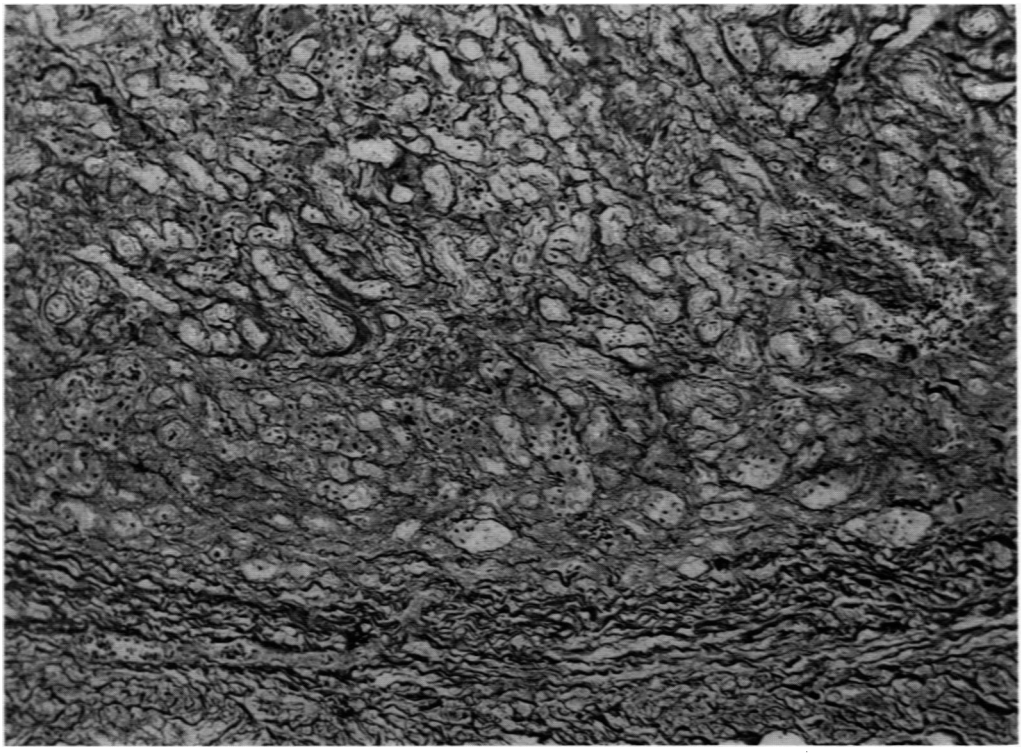

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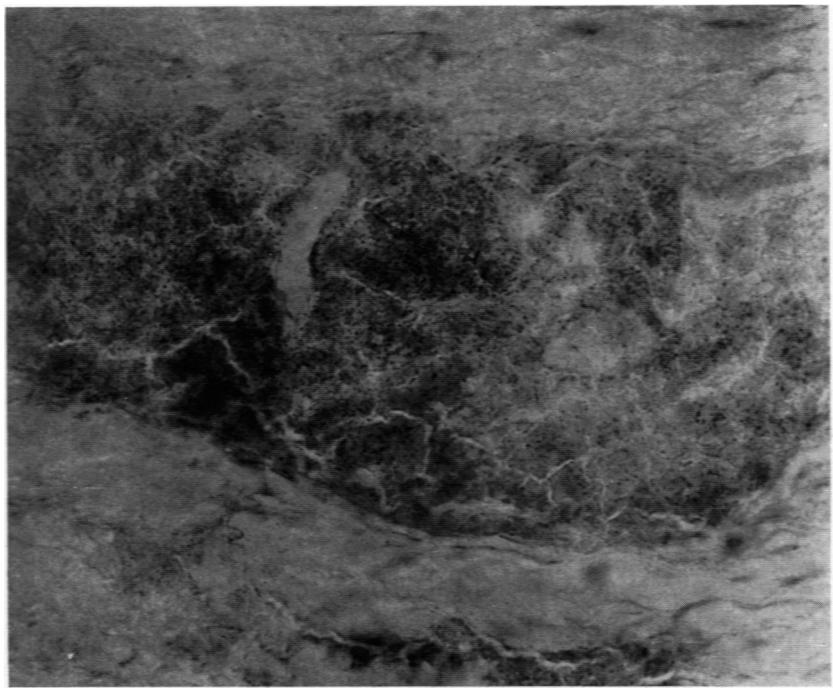
FIG. 9. Carotid body tumor, showing histochemical reaction for cholinesterase. The dark punctate granules are within the neoplastic cells, whereas the surrounding fibrous tissue is free of dye granules. × 150.

FIG. 10. Carotid body tumor stained for phospholipid. Each tumor cell is filled with dark-stained granules. The clear area in each cell represents the unstained nucleus. × 200.



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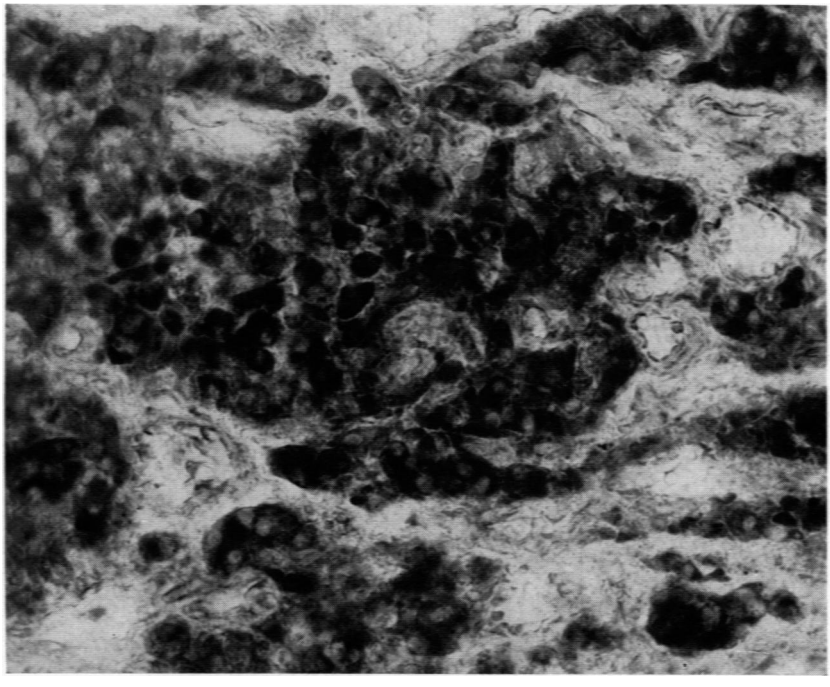

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