TUMORS OF THE CAROTID BODY *

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Tumors arising in the carotid body or glomus caroticum have been called by many names, including perithelioma, endothelioma, angioma, chromaffinoma, adenoma, paraganglioma, pheochromocytoma, and sympathoblastoma. The variety of names reflects the current confusion regarding the development, structure, and function of the carotid body. Accordingly, a consideration of some of the contemporary ideas on these subjects is in order.

Embryology

The carotid body was regarded by Kohn [25-27] as being derived from cells of the sympathetic nervous system and from the same anlage as the sympathetic ganglia. This concept has dominated the field until recent times, when considerable doubt has been cast upon it.

Smith [42] regarded the carotid body as a complex of elements which become associated during the developmental history of the third mesodermal arch. She indicated that mesodermal cells and neural elements from the glossopharyngeal, vagus, and sympathetic nerves might all participate. Boyd [4] emphasized a mesodermal condensation related to the third branchial arch artery and indicated his belief that these cells persist to form a considerable portion of the essential cells of the adult structure. He acknowledged also contributions from glossopharyngeal, vagus, and sympathetic nerves, but felt that these were of secondary importance.

The possibility that a few sympathetic cells are included in these bodies cannot be denied, especially since, as noted by Hollinshead,[19] the difficulties of following wandering embryonic cells in the region of the branchial arches are considerable. It seems probable, however, that even if migratory elements from the sympathetic ganglia are included in the carotid body, their rôle is a minor one.[4, 19, 42]

Anatomy

Grossly, the carotid body is a soft, but tough, ovoid, pale tan, rather poorly defined mass measuring about 5 by 3 by 2 mm. It is situated usually a little medial to and behind the bifurcation of the common

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carotid artery, being rather firmly bound to the vessels by loose fibrous tissue.

Microscopically, the tissue may be arranged in more or less distinct lobules (*e.g.*, cow, man) or in a compact mass (cat). The essential or "specific" cells are arranged in whorls or clusters (called "Zellballen" by Kohn [25]) which are completely surrounded by a supporting stroma exceedingly rich in capillaries (Figs. 1 and 2). This fundamental and characteristic structure is brought out clearly by silver impregnation of the reticulum (Fig. 3). The cells making up these clusters are round or polyhedral, resembling epithelium, with round or slightly oval nuclei containing fine chromatin particles. Their cytoplasm is abundant and may appear granular, vacuolated or reticular, depending in part upon fixation and technic. Cell boundaries are usually distinct, and there appears to be no good evidence that they ever form a syncytium. The presence of ganglion cells [15,33] has been seriously questioned by Hollinshead.[21]

The supporting stroma consists of fine collagenous and reticular fibers with innumerable capillaries. The endothelial cells of the latter are so large and numerous that some may appear to lie outside of the capillary lining (the so-called "perithelial" cells). Some of them are perhaps homologous with the "neuro-myo-arterial" cells of the cutaneous glomus.

In specially prepared sections, numerous nerve fibers are found. Thus, the principal constituent elements of the carotid body may be considered to be the "chief" or epithelioid cells making up the cell clusters, and the neural and endothelial elements (the latter perhaps including "perithelial" cells).

The Chromaffin Reaction

Much of the confusion regarding the nature of the carotid body and the histogenesis of its tumors arises from the use of the so-called chromaffin reaction. This refers to a yellowish brown color assumed by certain cells after fixation in fluids containing chromium salts. The prototype of this reaction is seen in the cells of the adrenal medulla, where the material taking the brown color is regarded as a precursor of epinephrine. Other cells giving the reaction are found in association with sympathetic ganglia, particularly in the abdomen.

Kohn [25] laid particular emphasis on the presence of the chromaffin reaction in some cells of the carotid body in various animals and regarded this as important evidence for his assumption of a sympathetic origin for the specific cells. Cells not giving the chromaffin reaction were regarded as of sympathetic origin nonetheless. Smith [42] and Boyd [4] found the chromaffin reaction to be present in a portion of the

cells of the carotid body in certain species (*e.g.*, cow, pig), but absent in others (*e.g.*, rat, man). DeCastro,[7,8] in a careful study, questioned the existence of a true chromaffin reaction in the carotid body and stated that the apparent reaction was due to the presence of lipoid substances in the cells. This conclusion was largely confirmed by Hollinshead,[21] who, however, felt that the cytoplasmic granules were not lipoid in nature, but might be mitochondria.

The chromaffin reaction has been clearly shown to be nonspecific. Indeed, the word "chromaffin" is a misnomer, since various oxidizing agents other than chromium salts will give the reaction.[12] Furthermore, organic substances other than epinephrine will form brown compounds when oxidized, *e.g.*, hydroquinone, resorcinol, aniline, various aldehydes and ketones, polyphenols, and polyamines.[1]

Innervation

The innervation of the adrenal medulla, with which Kohn[25] supposed the carotid body to be homologous, is motor and predominantly preganglionic. The carotid body, on the other hand, receives chiefly sensory nerves from the glossopharyngeal nerve.[7]

Function

The carotid body is sometimes referred to as a gland of internal secretion[11] or as having no known function.[43] The suggestion of DeCastro[8] that it is a chemoreceptor apparently has received abundant confirmation in the work of Heymans and Bouckaert,[18] of Schmidt and Comroe,[41] and of Dripps and Comroe,[9] who have shown that it and the similar cardio-aortic bodies are sensitive to changes in the pH, and in the carbon dioxide and oxygen tensions of the circulating blood, and that under certain conditions they may be of major importance in the regulation of respiration. It is also noteworthy that extracts of the carotid body have not been shown to contain epinephrine.[5]

Classification of the Carotid Body

Kohn's classification of the carotid body with the "paraganglia"[25-27] has had great influence down to the present day. Apparently he used the term to apply to collections of tissue associated developmentally with the sympathetic ganglia and homologous with the adrenal medulla. As noted by Hollinshead,[19] if this classification is to be acceptable for the carotid body, the latter should be shown to be similar to the adrenal medulla in development, structure, innervation, and function. However, as outlined above, the two structures appear to differ on all these counts. Similar observations apply to the aortic bodies or cardio-aortic bodies,[3,36,37] and it seems extremely doubtful that either they or the

carotid body should be included with the paraganglia. The propriety of regarding the carotid body as an arteriovenous anastomosis [15] or "glomus" is also questionable, since Hollinshead [20] has shown that it differs in vascular arrangement, innervation, and cytologic features from the glomus coccygeum, which presumably does represent a specialized arteriovenous anastomosis. It appears, therefore, that the carotid body, together with the similar cardio-aortic bodies, should be classified as a specialized chemoreceptor and not as a gland of internal secretion, paraganglion, or arteriovenous glomus.

Tumors

The present report is based upon 17 tumors taken from the files of the New England Deaconess Hospital and the Laboratory of Pathology of the Harvard Cancer Commission.* Without exception, they were removed surgically from the region of the bifurcation of the common carotid artery. In one case, only tissue taken for biopsy was available.

Gross Appearance

Weights were not recorded for most of the tumors. Three weighed 28, 50, and 60 gm., respectively. Measurements varied from 3 by 3 by 2 to 5 by 4 by 3 cm. In most cases the shape was globular or ovoid, a groove for the carotid artery sometimes being present if the artery had not actually been resected. In cases in which it was necessary to remove a segment of the artery, the neoplastic tissue was found to be closely adherent to the wall of the vessel. A well defined capsule usually was present. The color was recorded as pinkish gray to reddish brown. The tissue was usually firm and homogeneous.

Microscopic Features

Microscopically, most of the tumors showed a tendency to mimic the structure of the normal carotid body. The usual pattern was one of nests of the "chief" or epithelioid cells, fairly uniform in size, and surrounded by a vascular stroma similar to that of the normal organ. There was usually more variation in size and shape of the cells than in the normal gland. Mitotic figures were not observed. Generally speaking, the cell clusters of the tumors were larger than those of the normal organ (Figs. 4 and 5), and the supporting stroma was less cellular. The general pattern is best brought out by silver impregnation of the reticulum (Figs. 6 and 9).

For descriptive purposes, it was found possible to subdivide the tumors into three groups. The first, or *usual* type, included most of

* The clinical aspects of 15 of these cases have been reported separately by Lahey and Warren.[80]

the cases (12 tumors) and is the variety in which there is more or less faithful reproduction of the normal structure (Figs. 4, 5, 7, and 8). The second, or *adenoma-like* type (2 tumors), shows a pattern in which the chief cells have a pronounced epithelial appearance, with rounded or polyhedral shape, abundant cytoplasm, and arrangement in sheets or rows (Figs. 10 and 11). This appears to be the type referred to as adenoma by some authors.[11] In this type the reticulum is scanty. The third type may be called *angioma-like* (2 tumors). Here the cells are largely spindle-shaped or crescentic and apparently closely related to capillaries (Figs. 12 and 13).

In spite of these variations, however, the fundamental pattern appeared to be the same. The structural unit consisted of a group, of variable size, of the chief or epithelioid cells, surrounded by a more or less abundant vascular stroma. Most of the variations in microscopic appearance of the tumors seemed to be produced by differences in the shape of the chief cells. This in turn was apparently influenced to no small degree by such factors as clamping and squeezing the tissue during surgical removal, the time elapsing between removal and fixation, and the type of fixative. In many instances, more or less flattened or spindle-shaped cells were found in part of a tumor, while in better preserved fields the cells were plump and rounded. The mechanical factors involved in the growth of a well encapsulated tumor in an environment naturally restricted by dense fascial planes may also be considered as influencing the shape of the cells.

Most striking was the persistence of the general pattern of the reticulum in the majority of cases (Figs. 6, 9, and 13). Although the number of fibers and the size of the cell groups which they surrounded varied, the basic arrangement remained the same.

The Chromaffin Reaction

The cytoplasm of the chief cells was, in varying degrees, granular, vacuolated, or reticulated. Stains for fat and glycogen in several instances were negative. Vacuolation was often most marked in poorly fixed specimens. In many cases attempts were made to bring out a "chromaffin" reaction in the cells. In those cases in which fresh tissue was available, the technics described by Bennett [1] were used, such as fixation in formol-dichromate solution followed by mordanting for several days in 3 per cent potassium dichromate, and in some cases by "intensification" in Fontana's ammoniacal silver solution. When only fixed tissue was available, paraffin sections cut from formalin-fixed blocks were mordanted on the slide in 3 per cent solution of potassium dichromate, as recommended by Lison.[32]

In almost all instances, tissue treated with dichromate solution had

a faint yellowish color when compared with untreated tissue. However, this was never as striking as the color developed by the adrenal medulla under similar circumstances. Also the color of the neoplastic tissue was generally not more intense than that shown by sections of various other organs (*e.g.*, liver, heart, kidney) treated in the same way. No convincing evidence of a true chromaffin reaction could be found. The nonspecificity of the reaction has been commented upon above.

Assay for Epinephrine

Assays * for epinephrine were carried out on 2 of the tumors. In each case the fresh tissue was frozen solid within 2 or 3 hours after surgical removal and kept in that state until the assay was performed. This was done by extracting the tissue with 0.01 N hydrochloric acid and comparing the effect of this extract with a known solution of epinephrine. Tests were done on the blood pressure of the spinal cat and on the isolated strip of ileum of the rabbit. The first tumor (no. 76947) showed an activity equivalent to less than 8 γ of epinephrine per gm. of tissue, *i.e.*, a negligible amount. The second (no. 87076) was found to have an epinephrine-like action corresponding to about 0.4 mg. per gm. on the basis of blood pressure tests and 0.25 mg. on the basis of the test with the strip of ileum. The cause of the discrepancy between the two tumors was not apparent. Further tests on the second tumor, however, indicated that the pressor substance in question was probably not epinephrine.

Nerve Endings

An abundance of nerve endings has been demonstrated in the normal carotid body.[7,8] Apparently, nerve endings are absent in the tumors, although few attempts have been made to demonstrate them.[3] In one case in the series here reported, fresh tissue was fixed in 25 per cent chloral hydrate and impregnated according to one of the methods of DeCastro.† In one of several sections a few ill defined club-shaped structures were seen, but no definitely recognizable nerve fibers or nerve endings.

Evidence of Malignancy

None of the tumors showed evidence of malignancy. As noted above, practically all of the tumors were described as well encapsulated and as having a fairly smooth surface. Although many of the tumors were intimately adherent to the carotid arteries, no definite invasion of sur-

* I am grateful to Drs. Otto Krayer, Ralph Brauer, and Harriet M. Maling of the Department of Pharmacology of the Harvard Medical School for these assays.

† I am indebted to Dr. James Goddard for advice concerning this technic.

rounding structures was recorded in any case. In 5 cases, lymph nodes, varying in number from 1 to 6, were removed with the tumor mass. None showed microscopic evidence of invasion by neoplastic cells. No evidence of distant metastasis was present in any case.

Mitotic figures were not seen in any of the tumors. In 8 of 17 cases there was fairly marked variation in nuclear size (Fig. 14), with occasional giant forms.

Discussion

The ideas of Kohn [25-27] on the origin, structure, and function of the carotid body have dominated almost all discussion of the organ down to the present day. The important work of Hollinshead,[19-22] outlined briefly above, has been overlooked by even the more recent writers on carotid body tumors, with the notable exception of Bloom.[3] The physiologic evidence provided by Heymans and Bouckaert [18] and Schmidt and Comroe [41] has likewise not been emphasized. It seems clear from the work of these investigators that the carotid body is a chemoreceptor, not a gland of internal secretion; that its embryologic origin, while not entirely established, is probably not primarily from sympathetic elements; that it probably does not give a true chromaffin reaction, at least in man; that its innervation is primarily sensory; and that it does not secrete epinephrine.

There would appear, likewise, to be no satisfactory evidence that the tumors of the carotid body are derived from tissue of sympathetic origin. They resemble only superficially the pheochromocytomas of the adrenal medulla, and do not resemble at all the neuroblastomas of sympathetic origin.* Efforts to demonstrate the chromaffin reaction have been scanty and unconvincing. Most writers have been limited to formalin-fixed tissue and have regarded it as unsuitable for bringing out the chromaffin reaction, although in fact it is not.[32] Painstaking attempts like those of Bloom [3] (who failed to demonstrate the reaction) have been the exception rather than the rule. Likewise, efforts to demonstrate epinephrine by bio-assay or by chemical methods have met uniformly with failure, although a substance having a depressor effect on the blood pressure has been found [5] and in one of the tumors here reported a pressor substance of unknown nature was encountered (see above).

As for *nomenclature,* it would appear, in the light of available evidence, that terms such as "chromaffinoma," [14,34] "paraganglioma,"[16] and "adenoma" [11] are of doubtful propriety. The question whether

* The report by Cragg [6] of a carotid body tumor occurring simultaneously with tumors of the organs of Zuckerkandl is of great interest but can hardly be regarded as providing much evidence regarding the nature of carotid body tumors.

these tumors are to be regarded as hamartomas is raised by Kaufmann and Ruppanner,[28] and dismissed by the same authors because of the failure of investigators to demonstrate nerve endings in the tumors. The evidence in favor of the term "perithelioma" is discussed by Ewing.[10] However, the desirability of referring to the constituent cells as occurring "around blood vessels" when actually it is the blood vessels which surround nests of the "chief" cells, is open to question. As noted above, these cells probably may assume a spindle-like or flattened form resembling endothelium because of mechanical factors. Certainly they may, and do, take on a globular epithelium-like appearance in many instances. Also, the embryologic evidence is not in favor of an origin of these cells from endothelium or from adventitial cells in the walls of blood vessels.[4] The stroma of these tumors is admittedly exceedingly vascular, but, even in the "angiomatous" type described above, there seems to be no good reason for regarding it as essentially neoplastic or as differing in any important qualitative way from the stroma of other tumors. On the whole, it would appear that, unless the "chief" cells of the carotid body can be shown to be of the same nature as the "pericytes" of Zimmermann [47] and Stout,[35,44,45] the name "perithelioma" is of doubtful value. The suggestion of Bloom [8] that these tumors be designated by the noncommittal term "carotid body tumor" seems to be sound.*

Evidence of malignancy was, as noted above, singularly absent in the present series. Most of the tumors were well encapsulated, without evidence of invasion of adjacent structures, and none of the lymph nodes removed showed any tumor.†

It appears that the incidence of malignancy in these tumors may be overemphasized in the literature. I disagree vigorously with the thesis that 50 per cent of these tumors may be classified as malignant on histologic grounds.[17] While it is true that considerable variation in nuclear size, with the presence of giant forms, may occur (Fig. 14), such nuclear changes may be seen in other notably benign tumors, *e.g.*,

* Tumors of the homologous aortic bodies have not been reported in man, but Bloom [8] described two instances in dogs resembling the carotid body tumors of man. Following the report of Rosenwasser [40] of a tumor of carotid body type in the middle ear presumably arising from the "glomus jugulare," two other cases have been reported.[24,31] These tumors may cause extensive destruction of the mastoid bone and petrous ridge.[24,39] and one has apparently involved lymph nodes.[46]

† The only histologically malignant tumor of possible carotid body origin that I have seen is one sent by Dr. Paul Brindley of the University of Texas. It is a highly anaplastic sarcoma involving the region of the carotid bifurcation and, although its location is compatible with origin from the carotid body, the cells are so poorly differentiated that definite conclusions concerning histogenesis are impossible. In some fields multinucleated giant cells suggestive of myosarcoma are seen. As noted above, middle ear tumors of carotid body type may be at least locally invasive.

parathyroid adenomas. Mitotic figures are certainly the exception rather than the rule, and this is borne out by the frequency of prolonged clinical duration (up to 15 years in the present series).

Not a single case of visceral metastasis has been reported. (The case of Gilford and Davis [13] does not seem acceptable because of the lack of adequate illustrations.) The possible cerebral metastases recorded by Harrington *et al.*[17] are extremely questionable in the absence of autopsy evidence, and in view of the notoriously high incidence of cerebral sequelae following ligation or damage to the carotid arteries. Histologic evidence is notably lacking also in many cases in which the tumor is said to have recurred locally or to have extended upward to the base of the brain. The rate of postoperative recurrence is stated variously, being usually very low, but in some reviews fairly high.[38]

It is stated repeatedly in the literature that metastases to regional lymph nodes may occur. When, however, one attempts to find specific instances, the extreme rarity of metastasis becomes apparent. In an extensive, although not exhaustive, search of the literature, I was able to find only 2 cases [28,29] of histologically verified metastases in lymph nodes. In at least one of these,[28] the involved nodes were described as adjacent to the lower pole of the tumor and as being "infiltriert," apparently by direct extension.

The operative mortality is extremely high (about 30 per cent in the present series as well as others), due to the frequent necessity of ligating the carotid arteries in order to remove the tumor. In view of the clinically benign course of most of these tumors and the remarkable absence of symptoms in almost all cases, it would seem inadvisable to attempt surgical removal if it is necessary to ligate the carotids (admittedly it is sometimes impossible to gauge the feasibility of removal without ligation until the operation has progressed to such a point that it must be completed). The warning of Bevan and McCarthy [2] would seem to be still valid:

"With this evidence [about 30% operative mortality], we wish to present the conclusion that in the future neoplasms of the carotid body should not be removed when it is necessary to ligate the carotid arteries in order to complete the operation. If the common carotid and the internal carotid can be saved by careful dissection, done best under local anaesthesia, the removal of a benign tumor of the carotid gland would be justified. If the surgeon had definite and satisfactory evidence that the tumor was malignant, the huge 30 per cent mortality involved in the ligation of the carotid arteries might be accepted in order to save the patient from death and from malignant disease."

I would add that such "definite and satisfactory" evidence of malignancy is rarely available at the time of operation, or, indeed, subsequently.

SUMMARY

1. According to present evidence, the carotid body is a chemoreceptor, not a gland of internal secretion, and not part of the "chromaffin system."

2. In a series of 17 tumors of the carotid body no true chromaffin reaction was demonstrated, and no evidence for the secretion of epinephrine was obtained in assay of the fresh tissue in two instances.

3. Tumors of the carotid body exhibit a basic pattern of nests of "chief" cells surrounded by a more or less vascular stroma. Depending on the relative amounts of "chief" cells and stroma, they may be described as "usual," "adenoma-like," or "angioma-like."

4. Use of the non-committal term "carotid body tumor" is preferred to other names generally used.

5. The great majority of these tumors are both histologically and clinically benign. In view of the high operative mortality it is doubtful whether they should be removed in those cases in which ligation of the carotid arteries is necessary.

I am indebted to Drs. Shields Warren and Olive Gates for their interest and for making available the material on which this paper is based.

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DESCRIPTION OF PLATES

PLATE 60

FIG. 1. Normal carotid body. Phosphotungstic acid hematoxylin stain. × 400.

FIG. 2. Normal carotid body. In this instance the cells are better preserved and plumper than in Figure 1. Hematoxylin and eosin stain. × 400.

FIG. 3. Normal carotid body. The cell nests or "Zellballen" are clearly brought out. Same carotid body as used for Figure 2. Wilder's silver impregnation for reticulum. × 300.

FIG. 4. Carotid body tumor. The "usual" pattern, representing a slight exaggeration of the normal structure, with larger cell clusters. Phosphotungstic acid hematoxylin stain. × 400.

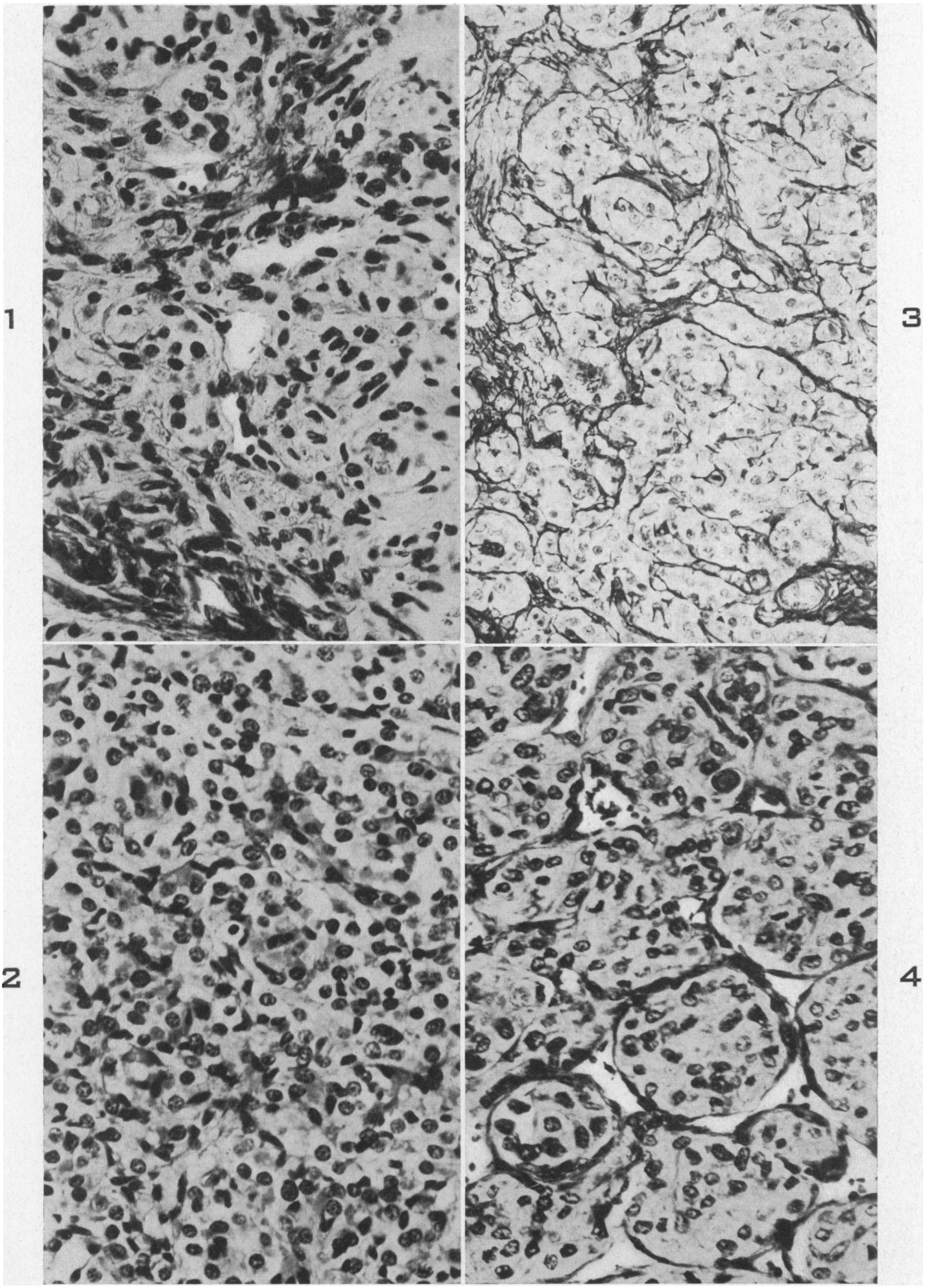
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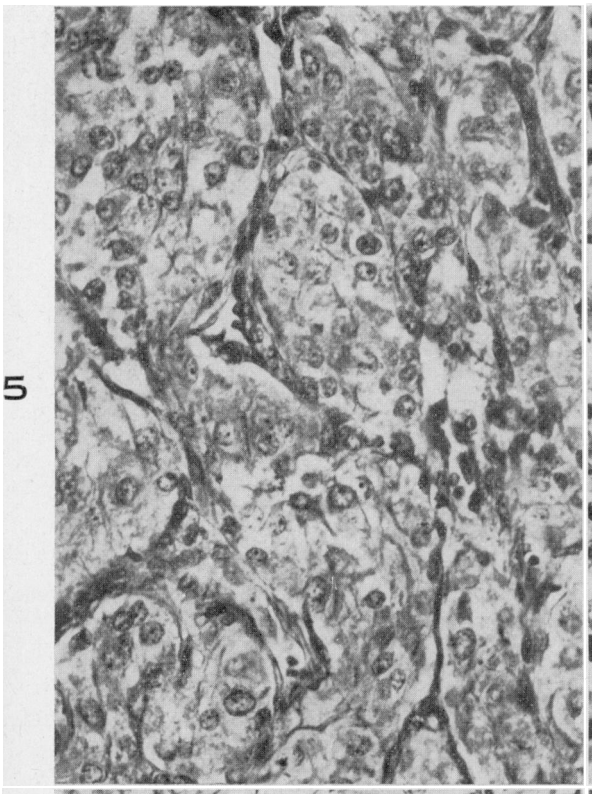
PLATE 61

FIG. 5. Another example of the "usual" type. Phosphotungstic acid hematoxylin stain. × 400.

FIG. 6. The characteristic reticulum pattern of a carotid body tumor. Same case as used for Figure 5. Foot-Bielschowsky stain. × 300.

FIG. 7. A variant of the "usual" pattern with somewhat smaller cell nests. Some of the dark material in the stroma is hemosiderin. Phosphotungstic acid hematoxylin stain. × 400.

FIG. 8. Another variant of the "usual" pattern. Rather poor preservation of the chief cells, with a tendency to elongated shape, perhaps an artifact due to compression. Phosphotungstic acid hematoxylin stain. × 400.



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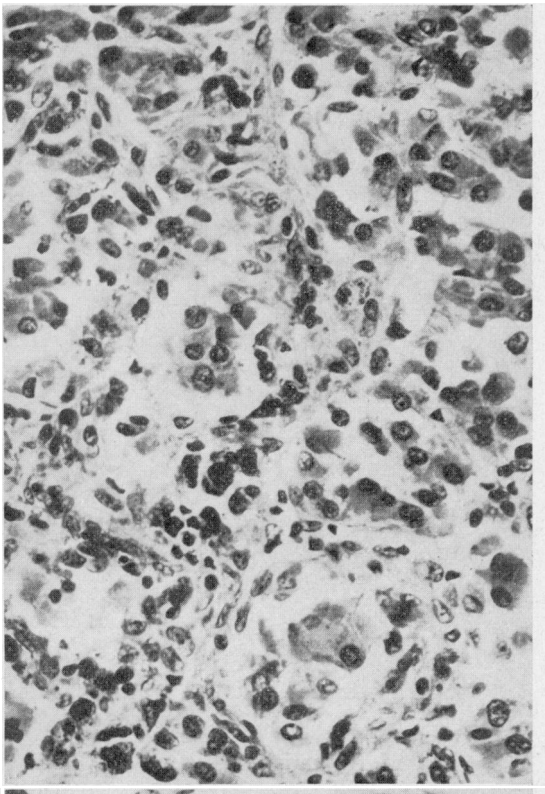

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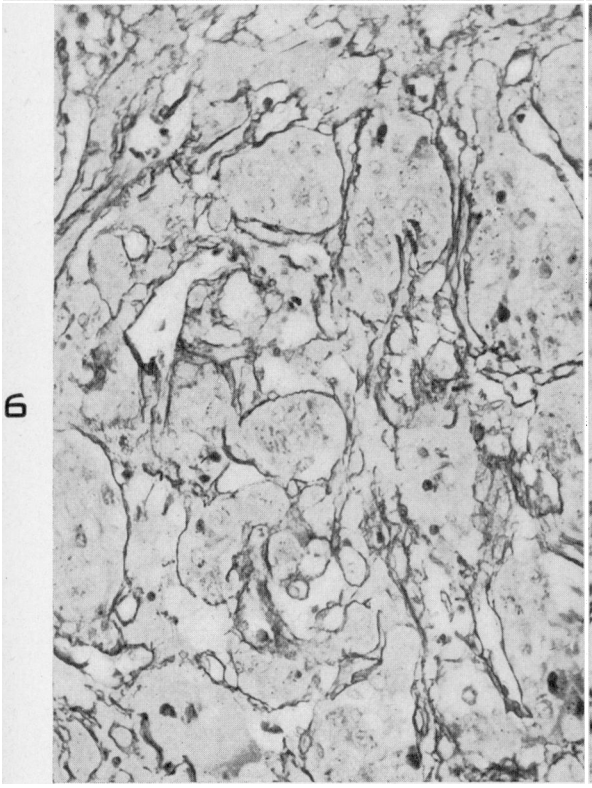

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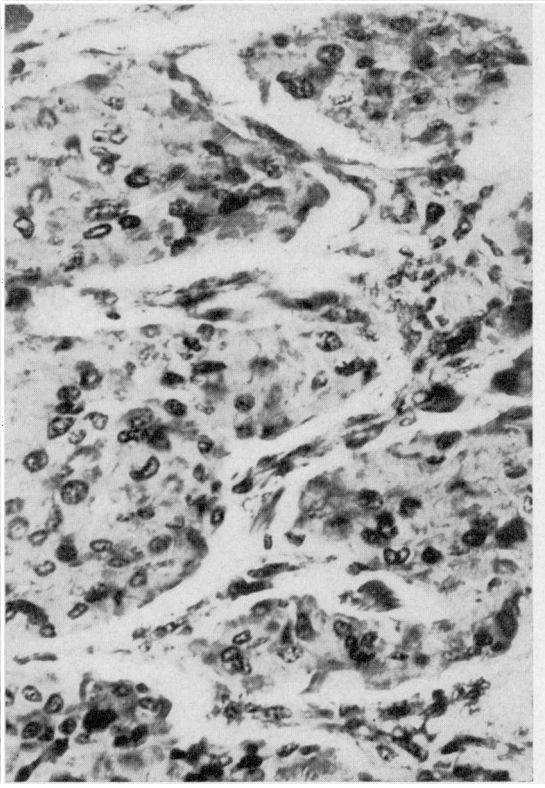

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PLATE 62

FIG. 9. Reticulum pattern of the tumor shown in Figure 8. The stroma is somewhat more abundant than usual. Wilder's silver impregnation. × 300.

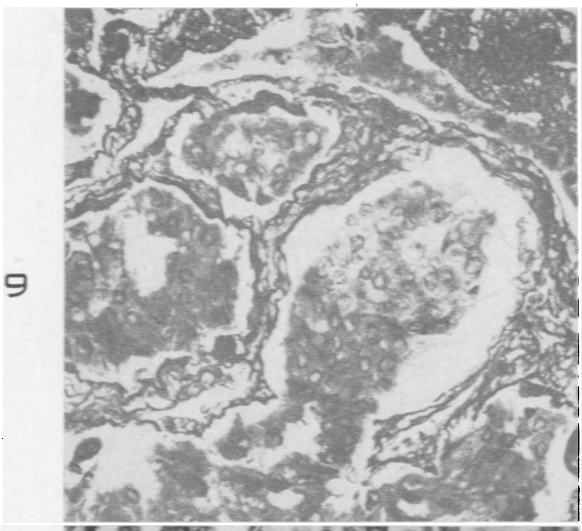
FIG. 10. The "adenoma-like" pattern. The chief cells have a strikingly epithelial appearance, but the arrangement of the "Zellballen" is maintained. Hematoxylin and eosin stain. × 400.

FIG. 11. A variant of the "adenoma-like" type. The chief cells are arranged in large sheets. Phosphotungstic acid hematoxylin stain. × 400.

FIG. 12. The "angioma-like" pattern. Here the chief cells are ovoid or spindle-shaped, and capillaries are numerous. Eosin and methylene blue stain. × 400.

FIG. 13. Silver impregnation (Wilder) of the tumor shown in Figure 12, showing that the fundamental structure is maintained, despite the angiomatous appearance. × 300.

FIG. 14. A tumor showing unusually marked variation in nuclear size, with one giant form. Hematoxylin and eosin stain. × 400.



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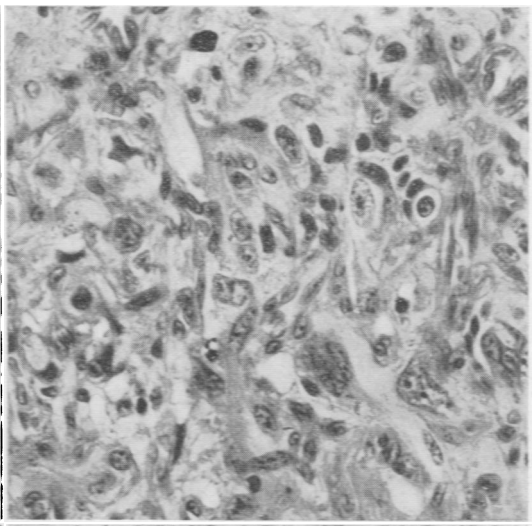

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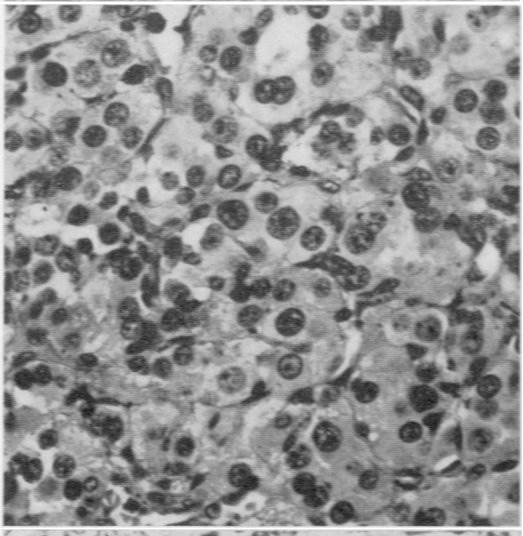

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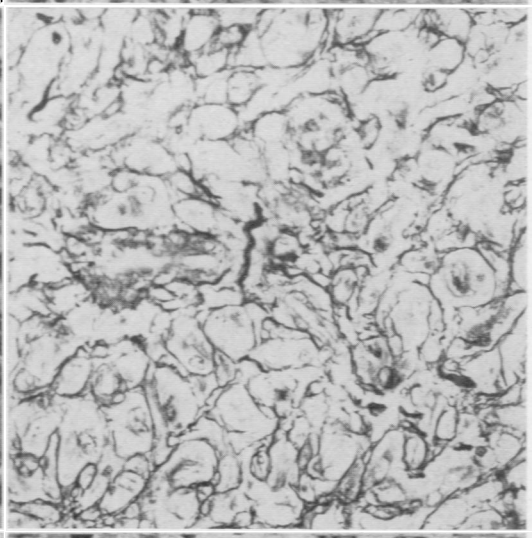

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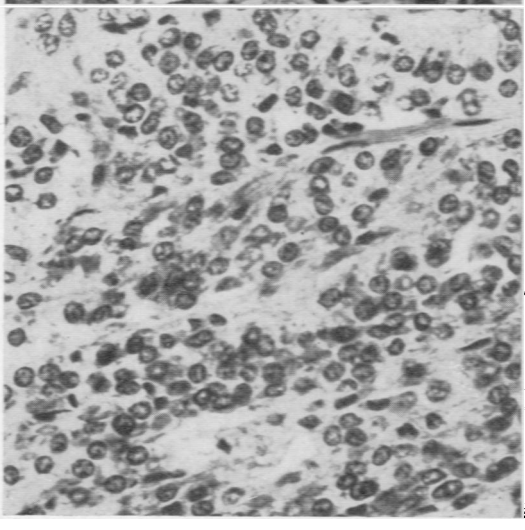

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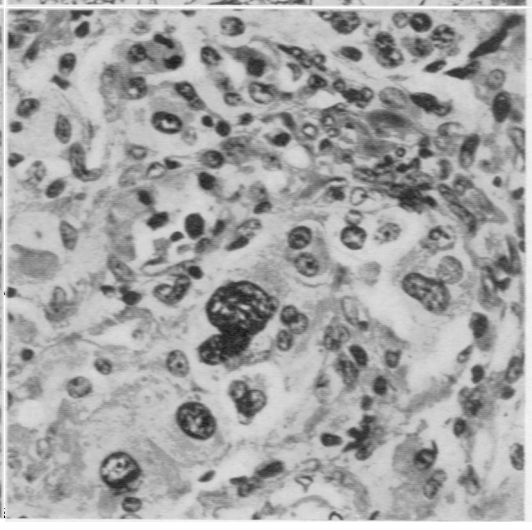

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