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Jugular Body Tumors: Hyperplasias or True Neoplasms?

Light and Electron Microscopical Investigations*

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Summary. Problems of classification of certain growth processes were discussed using jugular body tumors to find out cytological criteria for characterizing growth traits. For this purpose light microscopical (9 cases), electron microscopical (6 cases) and enzyme histochemical investigations (3 cases) were performed. For comparison 4 carotid body tumors were examined. We are inclined to assume a neoplastic nature. An explanation as hyperplastic proliferation is refuted because a remarkable cellular variation in size and form, only sparse nerve fibers and lacking synaptic contacts, because submicroscopical features and because the clinical picture and course of the disease. It is pointed to the origin of the tumor cells from rudimentary endocrine-like cells occurring in the glomus jugulare-tympanicum in analogy to other neoplasias. The clinical symptoms, the course and the pathologic anatomical pattern suggest an interpretation of jugular body tumors as potential malignant growths.

Zusammenfassung. An Hand von Paragangliomen des Mittelohres (jugular body tumors) werden Probleme der Klassifikation von Wachstumsprozessen erörtert. Im Vordergrund stand die biologische Einordnung dieser Tumoren. Dabei wurden zytologische Kriterien mittels lichtmikroskopischer (9 Fälle), elektronenmikroskopischer (6 Fälle) und enzymhistochemischer Methoden (3 Fälle) erarbeitet. Zum Vergleich wurden 4 Karotiskörpertumoren herangezogen. Als Ursache dieser Gewächse wird eine hyperplastische Proliferation abgelehnt. Die Annahme der neoplastischen Natur ergibt sich aus der zellulären Form- und Größenvariation, der Spärlichkeit von Nervenfasern und dem Fehlen von Synapsen, ferner aus submikroskopischen Befunden sowie aus dem klinischen Bild und dem Verlauf der Erkrankung. Der Ursprung der Tumorzellen wird auf rudimentäre, endokrinähnliche Zellen zurückgeführt. Damit besteht eine Analogie zu anderen Neoplasien. Die klinischen Symptome, der Verlauf und das pathologisch-anatomische Bild legen eine Interpretation der Paragangliome des Mittelohres als potentiell maligne Gewächse nahe.

Pathologists and clinicans are not seldom confronted with difficulties in distinguishing some growths when trying to put them into biological schedules. That comes true for some organoid hyperplasias, pseudotumorous lesions as well as autonomous tumors. It is the task of morphology to classify these processes in this difficult branch of oncology and to find out cytological criteria for characterizing growth traits. From this point of view it seems to be necessary to discuss these problems on the basis of an appropriate material. For this end we selected a group of lesions occurring in the middle ear which are designated by some scientists as benign lesions whereas other ones consider them as malignant growths.

* Presented to Prof. Dr. E. Uehlinger on behalf of his 75. birthday.

Lesions developing from glomus jugulare and tympanicum were termed glomus tumors, chemodectomas (Mulligan, 1950) or nonchromaffin paragangliomas (Lattes and Waltner, 1949). They were found as masses in the middle ear, but the exact point of origin could not be defined in each case (Schermer *et al.*, 1966). As a rule, the fact can be stated that tumors confined to the middle ear arose from the glomus tympanicum, true glomus jugulare tumors, however, are more likely to erode bone and cause neurologic symptoms. Taking into consideration our own studies we name these lesion "jugular body tumors" irrespective of their topographic relations within the middle ear. Thus we are in accordance with Schermer and coworkers (1966). These growths represent the second largest group of middle ear tumors after the carcinomas (Gejrot *et al.*, 1963) or even the most frequent tumorous lesion in this place (Brown, 1967).

In the paper presented we report the investigations on nine jugular body tumors without metastases using light and electron microscopical methods. For the latter method six tumors were available. Additionally, enzyme histochemical techniques were employed in three cases.

Material and Methods

For the light microscopical examination we employed nine jugular body tumors and, for comparison, four carotid body tumors. The material was fixed in 10% neutral formalin and embedded in paraffin. Sections 5 and 10 μm thick were cut and the following staining and histochemical reactions were used: Hematoxylin and Eosin, v. Gieson stain, Goldner trichrome stain, Giemsa stain, Congo red in the modification after Puchtler, Prussian blue, PAS, silver impregnation after Gomori for demonstration of reticular fibers, Bodian stain, proof of argyrophilic cells after Hellerström and Hellman, Sevier and Munger as well as Grimelius, proof of argentaffin cells by modification of the Masson-Hamperl method by Singh, acid hydrolysis followed by toluidine blue staining, and lead hematoxylin. Furthermore the fluorescence of unstained sections was controlled (references for methods see Capella and Solcia, 1971).

In three cases frozen sections were made and the reactivity of the following enzymes was tested: alpha-naphthyl acetate esterase, naphthol AS acetate esterase, acid phosphatase, alkaline phosphatase, ATPase and NADH diaphorase.

Additionally the material of six jugular body tumors was prepared for electron microscopical examination: fixation in 3% glutaraldehyde with 0.1 M cacodylate buffer at pH 7.2 (4 hours at 4°C), postfixation in osmium tetroxide, embedding in Vestopal and making of ultrathin sections. Contrasting with uranyl acetate and lead citrate.

1. 60-Year Old Woman. In 1970 radical operation of the left ear because of increasing hearing loss. At this operation a tumorlike change of the mucosa of the middle ear was found. In 1973 operative reexploration because of new complaints. The tumor was localized in the mesotympanon extending in the old operative cavity in the epitympanon and in the oval window niche. Auditory bones were completely destroyed.

2. 44-Year Old Woman. Since 1970 fullness and tinnitus in the right ear. Three years later slight hearing loss. Otoskopia revealed a reddish mass behind the inferior part of the intact tympanic membrane. At operation an intratympanous glomus tumor could be seen. It had connexion with the bulb of the jugular vene.

3. 32-Year Old Woman. Since 1969 tinnitus, a short time thereafter increasing hearing loss of the left ear. A pulsatile mass behind a fleshy tympanic membrane was visible. Operative extirpation of a tumorous mass which was localized in the hypotympanon.

4. 51-Year Old Woman. Two years ago beginning of increasing hearing loss and of attacks of severe aural pain in the right ear. At surgery a tumorous mass was found. This lesion occupied the whole right tympanon. The bulb of jugular vene was not involved. The complete removal of this lesion was possible.

5. 51-Year Old Woman. Since two years she has suffered from tinnitus and increasing hearing loss on the left side. At otoskopia a tumor was suspected. Consequently an operation was performed and a so-called glomus tumor was removed. This lesion was situated in the hypotympanon reaching the tubal angle.

6. 69-Year Old Woman. Pulsating mass behind the intact tympanic membrane, operative removal of an tumor localized preponderantly in the mesotympanon. Complete extirpation, no recidive.

7. 68-Year Old Woman. Since one year she noticed tinnitus and increasing hearing loss. Complete extirpation of a so-called glomus tumor.

8. 59-Year Old Woman. In 1961 attacks of moderate aural pain and tinnitus in the right ear. A pink pulsatile tumor was visible behind the tympanic membrane. Operative removal of a jugular body tumor. Thirteen years later recurrence of the tumor. The retroauricular radical operation yielded a typical jugular body tumor in the tympanon with enveloping of the facial nerve.

9. 44-Year Old Woman. Typical complaints in the right ear. At surgery a reddish jugular body tumor was extirpated.

Case Reports

Light Microscopy

All jugular body tumors investigated showed a common basic structural pattern revealing the typical pseudolobular picture: tumor cells were seen in an organoid arrangement often composed in clusters (so-called "Zellballen"), between them was a rich network of capillaries. The proportion and relation between these two components varied somewhat from tumor to tumor and in part also from area to area within the same tumor (Fig. 1).

The tumor cells partly possessed abundant, finely granular eosinophilic cytoplasm which gave them an oval, round or polyhedral shape resembling epithelium (Fig. 2a). However, the cytoplasm could also be vacuolized so that it appeared clearly (Fig. 2b). The cell borders were distinct. Other tumor cells were spindle-shaped with indistinct cell borders. If typical cell clusters were present the centrally located cells were to be discerned in a roundish shape, the cell layer forming the edge consisted of crescent-shaped cell elements (cp. Fig. 1c and d). The nuclei varying from round to oval exhibited a slight pleomorphism in most of the cases, only infrequently they were completely uniform in size and shape (Fig. 3b and c). Sometimes cells with two nuclei could be observed, whereas giant nuclei or multinucleated giant cells were not present. Mostly nucleoli were inconspicuous. Mitoses were rare.

The tumor cells always showed particular relations to the blood vessels in that they were arranged in close vicinity to capillaries. As a rule the cell clusters were surrounded by capillaries. If regular cell conglomerates were not formed so clearly the tumor cells could be seen more in sheets, however never leaving the close contact to the surrounding blood vessels. Although the histological pattern of juguar body tumors did not demonstrate complete identity, a differentiation into three types according to LeCompte's (1951) classification of carotid body tumors was not possible without arbitrariness. On the basis of the number of capillaries and venous vessels only a subdivision into cellular and vascular forms seems to be possible.

Argyrophilic cells were localized within cell clusters, but not all cells were reactive (Fig. 3a). The methods for proof of argyrophilia did not give convincing

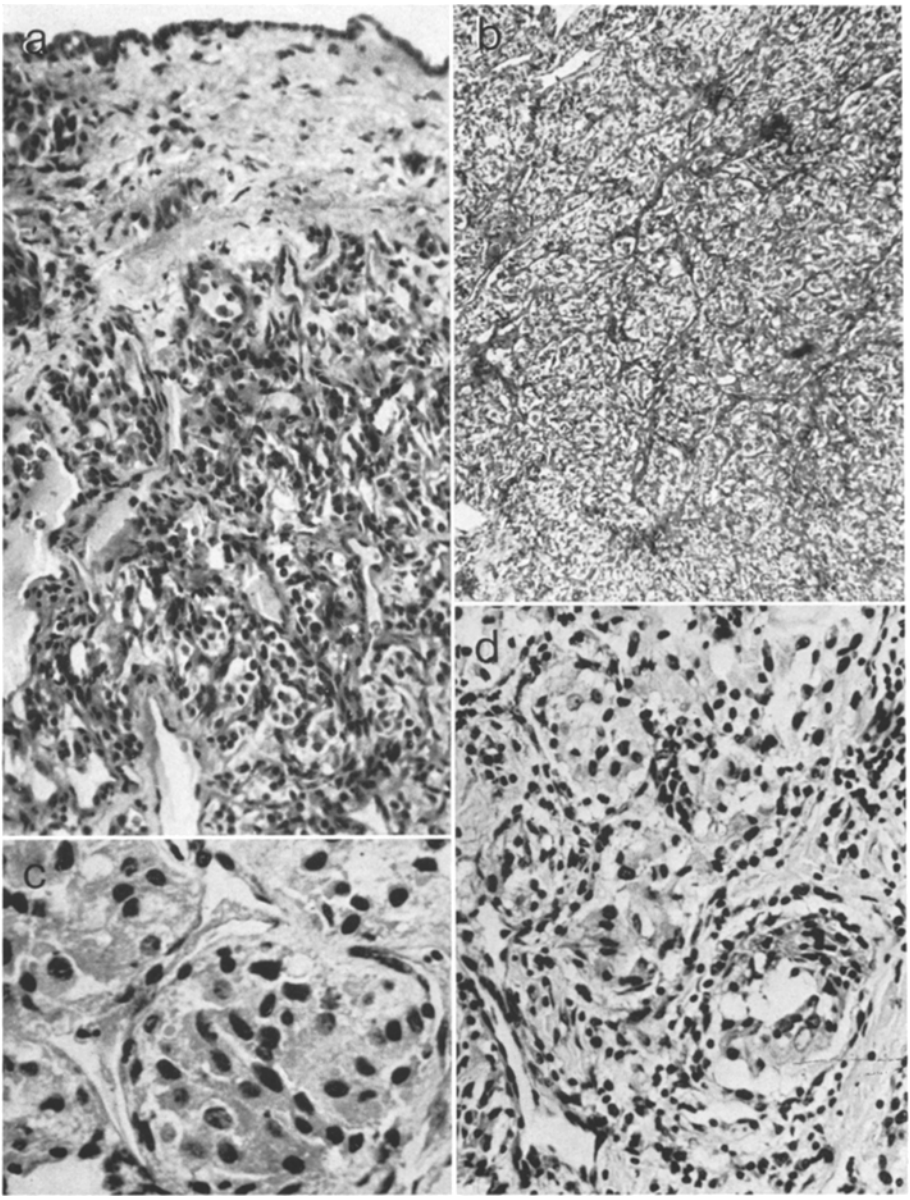

Fig. 1a—d. Demonstration of varying histological appearances of jugular body tumors. (a) Low power micrograph shows the predominant vascular basic structure. Tumor tissue is surrounded by a fibrous tissue covered by normal mucosa (HE, 200:1). (b) Example for a so-called cellular form mimicking an endocrine pattern (HE, 80:1). (c) Cell clusters (so-called "Zellballen") with crescent-shaped cells on the edge. Interstitial connective tissue is sparse (HE, 300:1). (d) Less uniformity of the tumor cells with remarkable cytological differences. Inflammatory cells within the stroma (HE, 200:1)

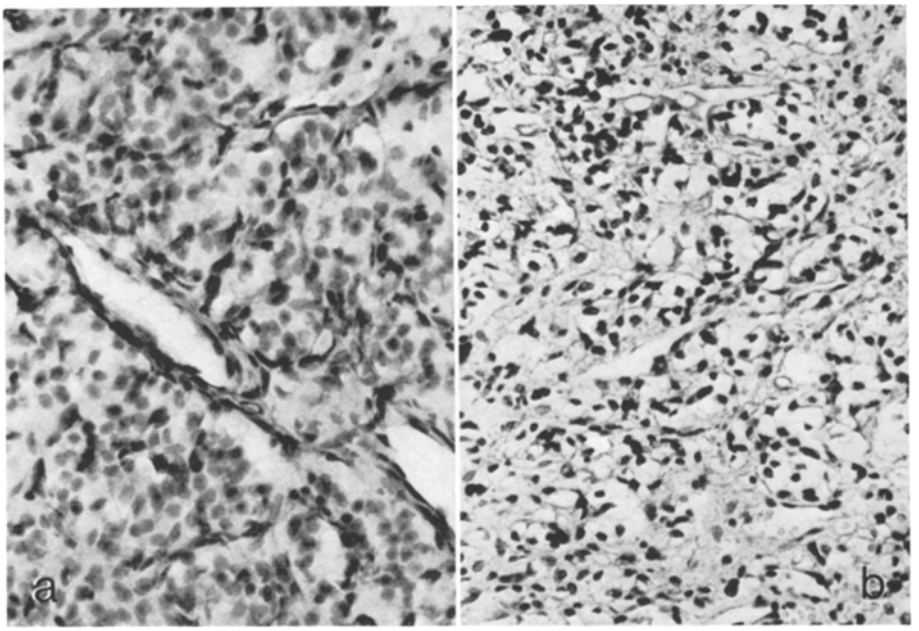

Fig. 2a and b. Comparison of the two tumorous chief cell types: cells with eosinophilic cytoplasm [dark cells (a), HE, 200:1] and with clear cytoplasm [light cells (b), HE, 200:1]

results in all cases, obviously this fact was caused by technical reasons. Argentaffin cells were absent. We did not succeed in proving lipofuscin with light microscopical methods, only scanty nerve fibers were to be demonstrated. Staining with lead hematoxylin and toluidine blue metachromasia preceded by acid hydrolysis made visible that only a part of cells was positive again.

Concerning the local behaviour of tumors, i.e. presence of infiltration or not, the evaluation of the material was not without difficulty because of the cutting into small pieces during the operative removal. Mostly we could evidence the infiltrative growth into the neighbouring connective tissue. Sometimes a pseudocapsule consisting of compressed connective tissue was found, true capsule formation was always missed. Occasionally scattered inflammatory cells were to be seen, also iron storing macrophages in the perivascular interstitial tissue suggesting preceding hemorrhages were present.

The four carotid body tumors evaluated for comparison were structured in a similar fashion, i.e. they showed the organoid pattern described. The pleomorphism of nuclei was more strongly marked. One case with distant metastases, however, revealed the pattern of an undifferentiated malignant epithelial tumor in places. In other areas the resemblance to an organoid paraganglioma was only superficial.

The *enzyme histochemical* examinations performed supplementarily verified a principally similar pattern of reactions. Nonspecific esterases and NADH diaphorase were present as shown by their typical reaction products. Acid phos-

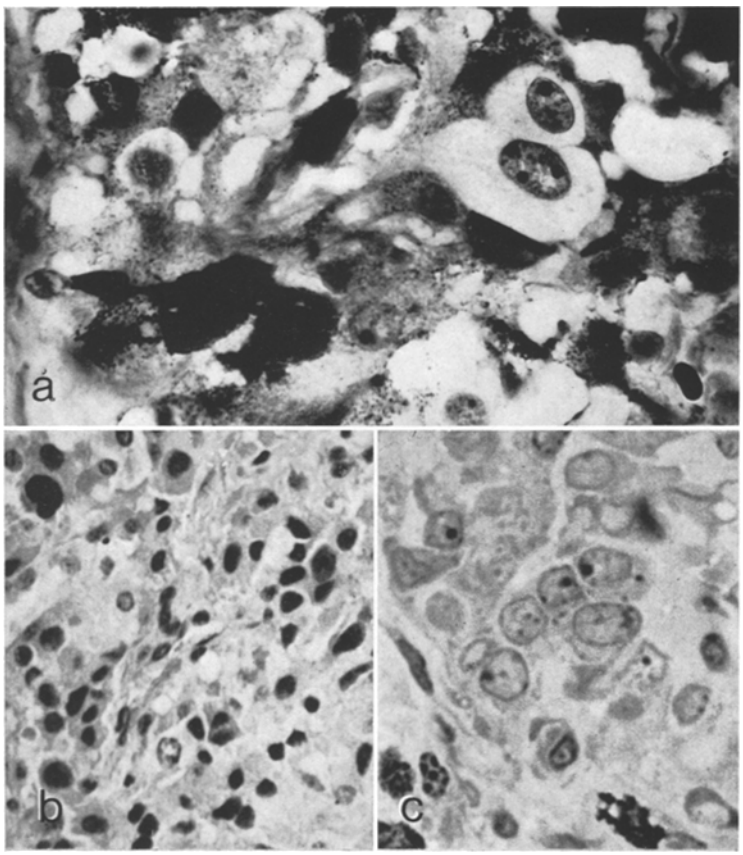

Fig. 3. (a) Silver impregnation after Hellerström and Hellman reveals different results: some cells are strongly positive, other ones without silver granules (1200:1). (b) Illustration of anisonucleoses, but bizarre nuclei are absent (HE, 300:1). (c) In the semithin section distinct nucleoles are visible, the nuclei are round or slightly indented. Different cell types in the surrounding connective tissue (mast cells, fibroblasts) (toluidine blue, 800:1)

phatase was weakly positive in places. Alkaline phosphatase and membrane bound ATPase were not to be demonstrated.

Especially in case 5 where the cell clusters could be observed very distinctly cells located in the periphery of the cell complexes were stronger positive with regard to the nonspecific naphthol AS acetate esterase. Additionally, this esterase seems to be distributed unequally in this case: some cells located randomly in the cell clusters hardly reacted with the substrate. This finding can also be established in other lesions, however in a minor degree. The tumor cells are

Fig. 4. Electron micrograph of a cell cluster. Changing organelle content permits the differentiation into dark and light cells. The nuclei possess a varying chromatin distribution. In the center an onion-like structure consisting of endoplasmic reticulum, and a nonmyelinated nerve fiber are visible. Varying content of osmiophilic secretory granules (18000:1)

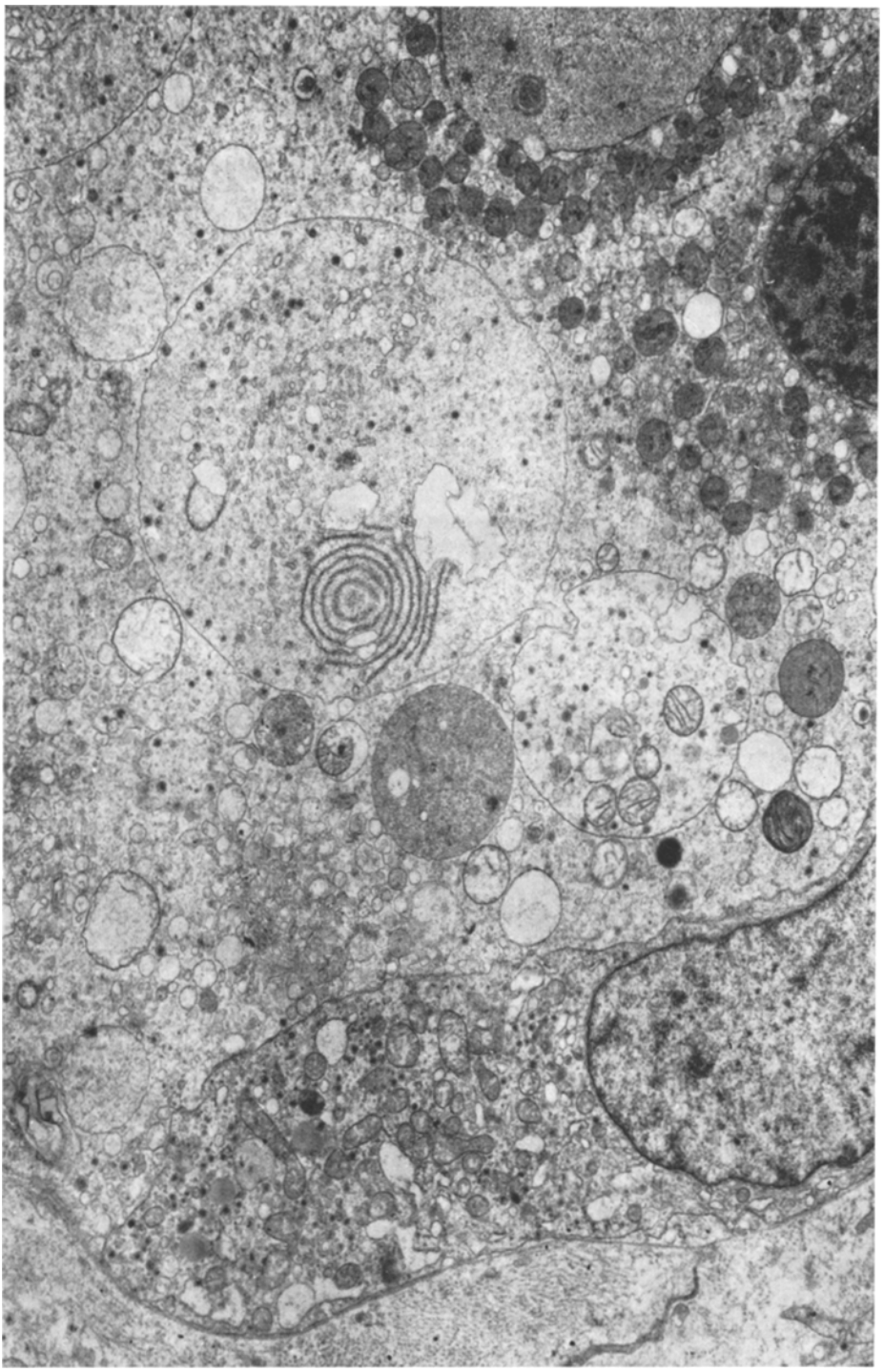

Fig. 4

uniformly equipped with NADH diaphorase, the enzyme activity was high (Fig. 7b).

Electron Microscopical Studies

Ultrastructurally different cell types could be easily differentiated: tumor cells whose features were very similar to the chief cells, and so-called sustentacular cells as well as cells of the local supporting tissue. As could already be seen in the light microscope the tumorous chief cells were mostly located in clusters (Fig. 4). They were surrounded by sustentacular cells or if abutting upon interstitial tissue by a basement membrane-like material (Fig. 5a). Sometimes their cytoplasm formed blunt processes interdigitating in complex fashion among themselves (Fig. 5c). Parts of cell surfaces, however, are smooth showing segmentally specialized intercellular junctions which could be identified as desmosomes (cp. also Gonzalez-Angulo *et al.*, 1968). The sustentacular cells possessed elongated slender cytoplasmic processes with tendency for enveloping the chief cell clusters. Within the stroma there were scanty non-myelinated nerve fibers in some cases (cp. Fig. 4). Synaptic contacts were not seen. Other tissue components of the tumors were vascular channels composed of typical endothelial cells, basement membranes and surrounding pericytes (Fig. 6). Moreover, intercellular ground substance together with fibroblasts and connective tissue fibers and scattered neutrophil granulocytes could be seen in places. Some macrophages with or without hemosiderin granules and lipids were detectable as well.

A recognition of two tumorous chief cell types was possible occasionally: a "light" and a "dark" one. But the surgical ischemia causing watery degeneration of cells rendered a clear distinction more difficult. Generally, they possessed a similar organelle equipment, only the quantity of these organelles was different in that the light cells contained less organelles (Fig. 4). The nucleus was round to ovoid not seldom moderately indented. Occasionally anisonucleoses could be detected. Bizarre nuclei previously noted in carotid body tumors (LeCompte, 1951) were not to be discovered. The heterochromatin was dispersed in coarse deposits or irregular clusters displaying a stippled pattern. Some nuclei showed a much finer chromatin distribution (cp. Fig. 4). In those nuclei there were some intranuclear spherical dark zones about 300 μm in diameter which consisted of a central dense core and two concentric lamellae around it (Fig. 5d). These formations were strikingly similar to those in chief cell nuclei of guinea pig's carotid body (Kondo, 1971) and in nuclei of other tumor cells. The nuclei contained one, occasionally two small nucleoli. Irregularities in the nuclear envelope were frequently observed probably the result of surgical ischemia preceding fixation. The cytoplasm was characterized by the presence of membrane-bound osmiophilic granules with rounded profiles. Their diameters were partially due to the plane of section and varied between 70 and 200 μm (Fig. 5e and f). Nevertheless the granules impressed by their relative uniformity. The granule matrix appearing as dense structureless mass or as a finely granular material was often separated from the limiting membrane by a clear zone or halo measuring 10–20 μm in its average width. Occasionally, a hollow core in the granules could be observed (Fig. 5f). Some tumor cells devoid of granules were also found and in some fields isolated cytoplasmic structures were identified scattered throughout the

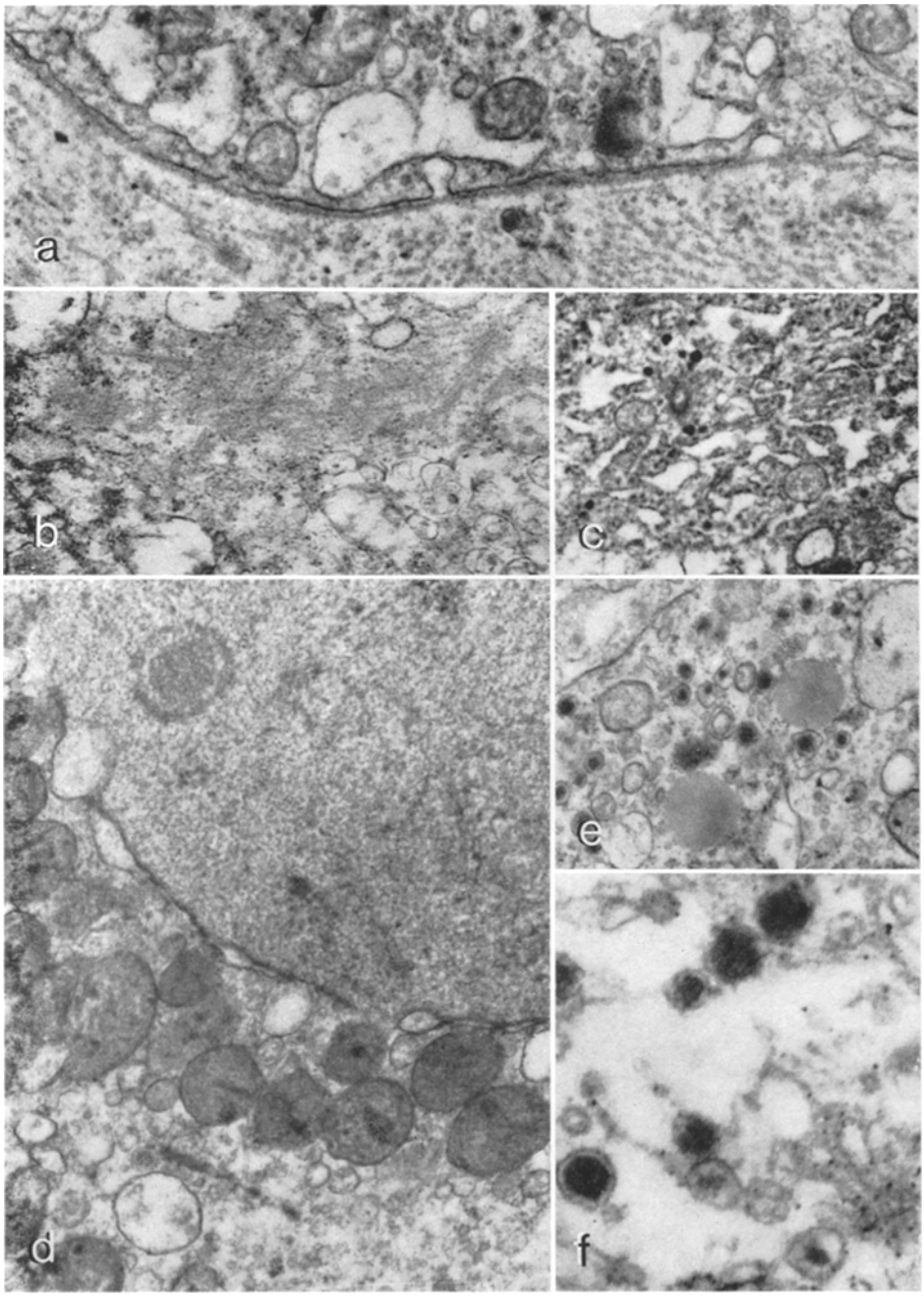

Fig. 5a—f. Examples for different ultrastructural features. (a) Separation of a tumor cell from the surrounding connective tissue by a basement membrane-like material (detail from Fig. 4 — 11800:1). (b) Microfilaments in the cytoplasm of tumorous chief cells (24000:1). (c) Interdigitating of two tumor cells by blunt processes (13200:1). (d) Spherical inclusion body (so-called target body) with concentric lamellae and a dark core within a nucleus of a dark cell (detail from Fig. 4 — 23400:1). (e) Many osmiophilic secretory granules and lipid droplets in the tumor cell cytoplasm (22800:1). (f) Secretory granules with varying content of osmiophilic material, some granules show a large dense core, other ones are hollow, transition stages are also visible (52800:1)

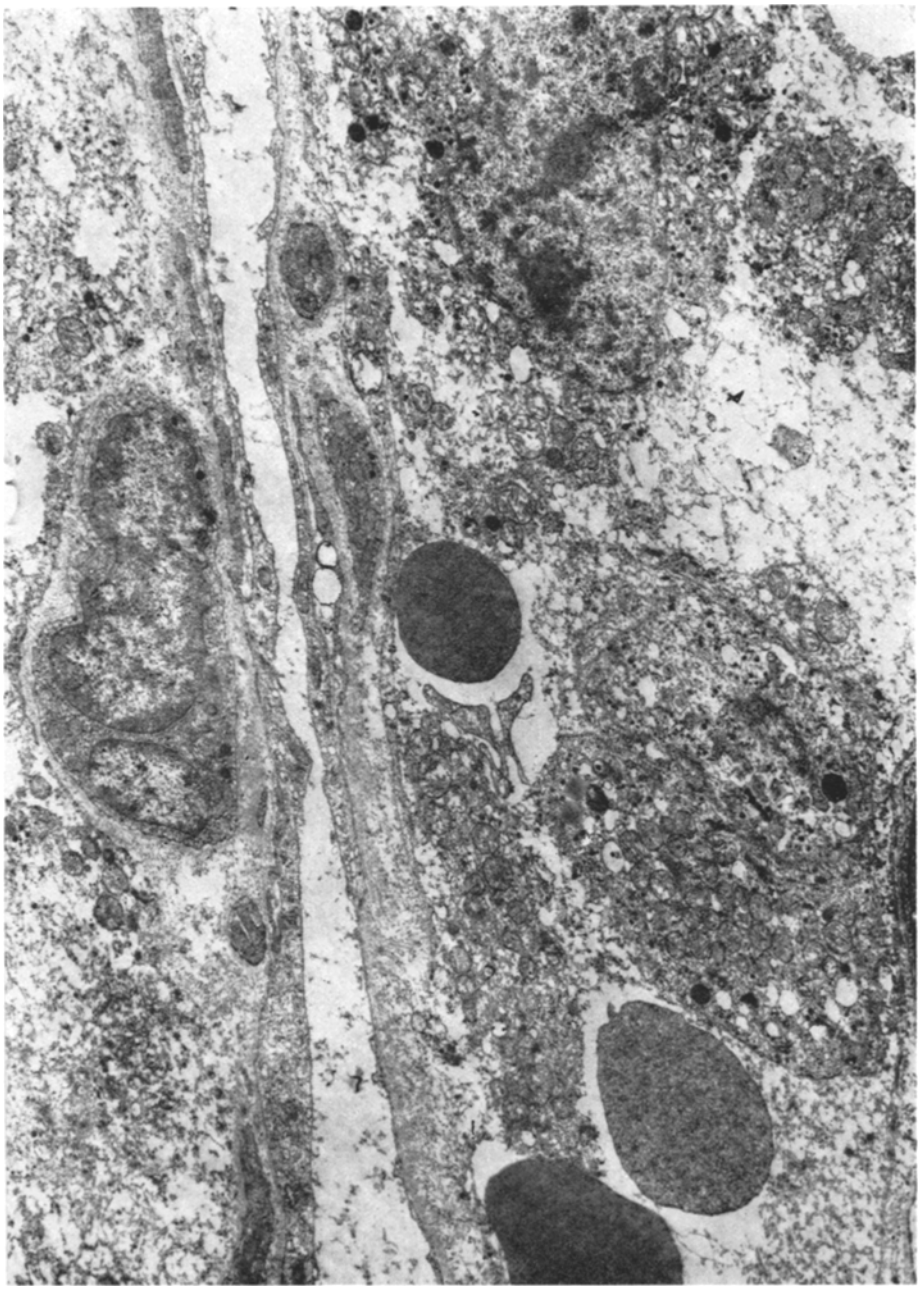

Fig. 6. Tumor cells with secretory granules and a capillary can be seen. The erythrocytes in neighbourhood of the capillary are artificially dislocated at surgery (9000:1)

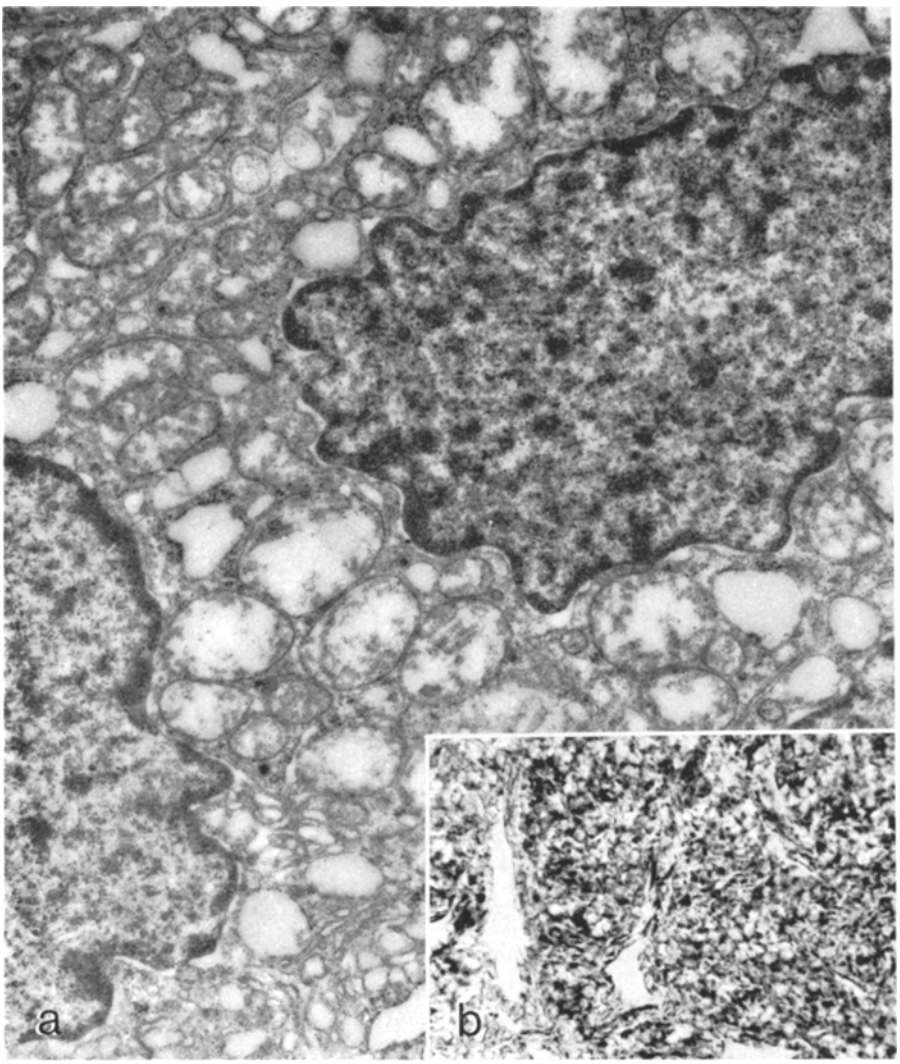

Fig. 7. Tumor cells rich on mitochondria (a, 21600:1) and also on NADH diaphorase (b, 300:1) are shown. Note the sparcity of secretory granules, the multicentric Golgi apparatus and the indented nuclei. Swelling of mitochondria is caused by surgical ischemia

stroma. Mitochondria exhibiting a round or ovoid and sometimes an irregular worm-shaped form were partly present.

In several cells the mitochondria were tighly packed so that oncocytic cells of endocrine tumors were mimicked. Within these cells only sparse secretory granules were to be seen (Fig. 7). Clear vacuoles as well as swollen mitochondria should be related to surgical hypoxia. Mitochondria in dark cells seemed to be less sensitive to anoxia in comparison to those in light cells commonly observed in a

hydropic state (cp. Fig. 4). The reverse observation was made by Qizilbash (1973) in the case of a paraganglioma of the duodenum. However we must mention that the cells with a very great number of mitochondria form an exception from the observation reported before, in that they are markedly sensitive to anoxia (Fig. 7). Rough endoplasmic reticulum was not conspicuous, seldom onion-like structures were noticed (Fig. 4). Polyribosomes could be seen here and there. Golgi complex was principally well developed and not infrequently multicentric (Fig. 7a). In some membrane-limited vacuoles electron dense granules or mitochondria were demonstrable speaking for their lysosomal nature. Moreover, there were dense bodies in the cytoplasm representing obviously lipids. In two cases microtubules and microfilaments arranged in a random fashion could be demonstrated in the cytoplasm (Fig. 5b).

The sustentacular cells in the typical fashion could only rarely be identified Their cytoplasmic processes contained often abundant granular endoplasmic reticulum and resembled fibroblasts also concerning to the nucleus structure. Pigment densities of residual type (lipofuscin) were sporadically visible similar to the carotid body tumors described by Grimley and Glenner (1967). Microtubules and filaments characteristic for sustentacular cells were seldom detected.

Discussion

Our findings prove the high differentiation on cytological level and the formation of a characteristic histological pattern. Ultrastructurally typical features are the secretory granules and a great content of mitochondria in many cells which points to a distinct activity of metabolism. With this conclusion the demonstration of a hypertrophied Golgi apparatus is in accordance.

Furthermore, the growth to be clinically observed is not correlated to the increase of the cell number only, but is also caused by an enlargement of the specific cells in comparison to normal glomus cells.

Consequently characteristics common for hyperplasias as well as true tumors are present. This demands a decision on the nature of the growths of the jugular and tympanic body. We are inclined to assume a *neoplastic nature.*

Our postulate is firstly based on the remarkable growth of tumorous chief cell-like cells showing up variations in size and form more than in the normal state (Moore *et al.*, 1973), whereas only scanty nerve fibers and sustentacular cells and no synaptic contacts could be demonstrated (cp. Grimley and Glenner, 1967). Secondly the elaboration of fine microfilaments supports the concept of the neoplastic nature (Pearse, 1969). Thirdly this theory is strengthened by the existence of so-called target-bodies (Luse, 1961) and fourthly by the clinical picture and course of the disease.

Although the function of the carotid body as chemoreceptor is widely accepted (see Pollack, 1973; Totten, 1973) this is proved by no means for other paraganglia especially the jugular and tympanic bodies. The true function of the latter organs if such is existing at all is not known. Zettergren and Lindström (1951) even regarded these structures as rudiments having their major importance in forming the site of origin of middle ear tumors. In our opinion a similar mechanism comes true for the histogenesis of adenomas and also oat-cell carcinomas of the

bronchus. The ancestral cells regarded as neural crest derivatives remain in a functionless state in adult persons (Hachmeister and Okorie, 1971; Moosavi *et al.*, 1973), i.e. these cells must be considered as rudiments and in the case of neoplastic proliferation they have not got to exercise their ontogenetically determined function.

The same considerations are valid for jugular body tumors. The tumor cells exhibit secretory granules round without significant form variation in contrast to other "endocrine" cells (Ferreira, 1971; Hage, 1973). These granules resemble those in nerve endings of sympathetic nerve fibers (Gejrot *et al.*, 1963), i.e. structures known to produce catecholamines. Catecholamines were in fact evidenced in jugular body tumors (Balogh *et al.*, 1966; DeLellis and Roth, 1971). A clinical reflection of a catecholamine secretion, however, did not exist in our cases as shown by the clinical courses. Likewise, Fuller and his collagues (1967) could not give certainty on a true relation between hypertonia and jugular body tumors. Other authors described an increased urinary excretion of noradrenaline (Levit *et al.*, 1969). An associated clinical syndrome basing on a secretion by tumor cells is not known till now.

If further investigations should ascertain a function of normal jugular or tympanic bodies (cp. Böck, 1974), then the interpretation of some corresponding tumors as hyperplasias and/or hyperplasiogenic growths might be possible. In this case the conditions might be comparable to carotid body tumors, which are considered as true neoplasms warrantable when metastases are produced (Pryse-Davies *et al.*, 1964; Hamberger *et al.*, 1967; Schwingshackl *et al.*, 1973; Villiaumey *et al.*, 1974), or as hyperplasias when occurring in association with other endocrine (and non-endocrine) hyperplasias (Pollack, 1973), multiple (Westbrook *et al.*, 1972) and/or under hypoxic conditions (Saldana *et al.*, 1973). First observations of bilateral glomus tumors are already documented in literature (House and Graham, 1973).

Evaluating our findings with regard to the classification of the presented cases as tumors or hyperplasias, the observation that several tumor cells harbouring abundant mitochondria possess only a few secretory granules must be emphasized. The visualization of this phenomenon was attained with the electron microscope, but the moderate argyrophilia known to be correlated to the polypeptide-producing potential of the cells (Roediger, 1973) was already suspect of such a finding. But a hyperplastic growth should in abundance produce the functional structures answering the hyperplastic stimulus. The review of the literature yielded numerous publications which strengthen the concept that jugular body tumors have a cellular origin histogenetically related to all other paragangliomas in that the stem cells of these tumors are of neural crest origin. Therefore the light microscopical similarity, for example, between jugular and carotid body tumors is not surprising (Hatfield *et al.*, 1972). But the structural variations of the carotid body tumors seem to be more obvious than in jugular body tumors. The application of histochemical methods confirms that no complete identity exists. The possible absence of argentaffin cells demonstrated in our and other cases (Pryse-Davies *et al.*, 1964) are in contrast to the invariable presence of argentaffin cells in carotid body tumors (Barroso-Moguel and Costero, 1962). In the same sense the often reduced number of secretory granules and the weak reaction with lead hematoxylin and toluidine blue preceded by acid hydrolysis must be stressed. Therefore the comparison with other paragangliomas is not permitted unreservedly.

That is also expressed by the clinical course though no specific histological criterion can be made liable for predicting the proper behaviour (Pryse-Davies *et al.*, 1964). Jugular body tumors in the middle ear must be considered clinically malignant (LeCompte, 1951). Their growth is locally aggressive and invasive, relentless and spontaneous regressions are always lacking. Furthermore it is to be pointed to the pronounced tendency to formation of recidives (Hatfield *et al.*, 1972). Last not least, the potency to formation of metastases is well documented (Rosenwasser, 1968; Spector *et al.*, 1973; further references see Moore *et al.*, 1973). The clinical symptoms, the course and the pathologic anatomical pattern suggest an interpretation of jugular body tumors as potentially malignant growths.

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References

Balogh, K., Draskóczy, P. R., Caulfield, J. B.: Norepinephrine in tumours of the jugular glomus. Amer. J. Path. **48**, 40a (1966)

Barroso-Moguel, R., Costero, I.: Argentaffin cells of the carotid body tumor. Amer. J. Path. **41**, 389–403 (1962)

Böck, P.: Das System der chromaffinen Paraganglien. Wien. klin. Wschr. **86**, 95–97 (1974)

Brown, J. S.: Glomus jugulare tumors. Methods and difficulties of diagnosis and surgical treatment. Laryngoscope (St Louis) **77**, 26–67 (1967)

Capella, C., Solcia, E.: Optical and electron microscopical study of cytoplasmic granules in human carotid body, carotid body tumors and glomus jugulare. Virchows Arch. Abt. B **7**, 37–53 (1971)

DeLellis, R. A., Roth, J. A.: Norepinephrine in a glomus jugulare tumour. Histochemical demonstration. Arch. Path. **92**, 73–75 (1971)

Ferreira, M. N.: Argentaffin and other "endocrine" cells of the small intestine in the adult mouse. I. Ultrastructure and classification. Amer. J. Anat. **131**, 315–330 (1971)

Fuller, A. M., Brown, H. A., Harrison, E. G., Sickert, R. G.: Chemodectomas of the glomus jugulare. Laryngoscope (St Louis) **77**, 218–238 (1967)

Gejrot, T., Lagerlöf, B., Wersäll, J.: Tumours of the glomus jugulare. A light and electron microscopic study. Acta oto-larying. (Stockh.), Suppl. **188**, 220–226 (1963)

Gonzalez-Angulo, A., Feria-Velasco, A., Corvera, J., Elias, E. Y.: Ultrastructure of the glomus jugulare tumor. Arch. Otolaryng. **87**, 12–21 (1968)

Grimley, P. M., Glenner, G. G.: Histology and ultrastructure of carotid body paragangliomas. Comparison with the normal gland. Cancer (Philad.) **20**, 1473–1488 (1967)

Hachmeister, U., Okorie, O.: Die Histogenese des kleinzelligen Bronchialcarcinoms. Verh. dtsch. Ges. Path. **55**, 716–721 (1971)

Hage, E.: Histochemistry and fine structure of bronchial carcinoid tumours. Virchows Arch. Abt. A **361**, 121–128 (1973)

Hamberger, C.-A., Hamberger, C. B., Wersäll, J., Wagermark, J.: Malignant catecholamine-producing tumour of the carotid body. Acta path. microbiol. scand. **69**, 489–492 (1967)

Hatfield, P. M., James, A. E., Schulz, M. D.: Chemodectomas of the glomus jugulare. Cancer (Philad.) **30**, 1164–1168 (1972)

House, W. F., Graham, M. D.: Bilateral glomus tumors of the temporal bone. Report of a case. Arch. Otolaryng. **98**, 58–59 (1973)

Kondo, H.: An electron microscopic study on innervation of the carotid body of guinea pig. J. Ultrastruct. Res. **37**, 544–562 (1971)

Lattes, R., Waltner, J. G.: Nonchromaffin paraganglioma of the middle ear. Cancer (Philad.) **2**, 447–459 (1949)

LeCompte, P. M.: Tumors of the carotid body and related structures (chemoreceptor system). In: Atlas of tumor pathology, sect. IV, fasc. 16. Washington: Armed Forces Institute of Pathology 1951

Levit, S. A., Sheps, S. G., Espinosa, R. E., Remine, W. H., Harrison, E. G.: Catecholamine-secreting paraganglioma of glomus jugulare region resembling pheochromocytoma. New Engl. J. Med. **281**, 805–811 (1969)

Luse, S. A.: Ultrastructural characteristics of normal and neoplastic cells. Progr. exp. Tumor Res. (Basel) **2**, 1–32 (1961)

Moore, G. R., Robbins, J. P., Seale, D. L., Fitz-Hugh, G. S., Constable, W. C.: Chemodectomas of the middle ear. A comparison of therapeutic modalities. Arch. Otolaryngol. **98**, 330–335 (1973)

Mulligan, R. M.: Chemodectoma in the dog. Amer. J. Path. **26**, 680–681 (1950)

Moosavi, H., Smith, P., Heath, D.: The Feyrter cell in hypoxia. Thorax **28**, 729–741 (1973)

Pearse, A. G. E.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. J. Histochem. Cytochem. **17**, 303–313 (1969)

Pollack, R. S.: Carotid body tumors—idiosyncrasies. Oncology **27**, 80–91 (1973)

Pryse-Davies, J., Dawson, I. M. P., Westbury, G.: Some morphologic, histochemical, and chemical observations on chemodectomas and the normal carotid body, including a study of the chromaffin reaction and possible ganglion cell elements. Cancer (Philad.) **17**, 185–202 (1964)

Qizilbash, A. H.: Benign paraganglioma of the duodenum. Case report with light and electron microscopic examination and brief review of the literature. Arch. Path. **96**, 276–280 (1973)

Roediger, W. E. W.: The nature of the silver binding in the canine thyroid "C" cell. S. Afr. J. med. Sci. **38**, 17–22 (1973)

Rosenwasser, H.: Glomus jugulare tumors: III. Clinical diagnosis. Arch. Otolaryngol. **88**, 11–15 (1968)

Saldana, M. J., Salem, L. E., Travezan, R.: High altitude hypoxia and chemodectomas. Human Path. **4**, 250–263 (1973)

Schermer, K. L., Pontius, E. E., Dziabis, M. D., McQuiston, R. J.: Tumors of the glomus jugulare and glomus tympanicum. Cancer (Philad.) **19**, 1273–1280 (1966)

Schwingshackl, H., Hörtnagl, H., Weiser, G., Glettner, M. A.: Maligner Tumor des Glomus caroticum mit Katecholaminsekretion. Dtsch. med. Wschr. **98**, 993–995 (1973)

Spector, G. J., Maisel, R. H., Ogura, J. H.: Glomus tumors in the middle ear. I. An analysis of 46 patients. Laryngoscope (St Louis) **83**, 1652–1672 (1973)

Totten, R. S.: Terminology of carotid body tumors: confusion at the crossroads (bifurcation). Human Path. **4**, 453–454 (1973)

Villiaumey, J., Amouroux, J., Rotterdam, M., Pointud, P., Delporte, M.-P.: Les métastases osseuses des chémodectomas du corpuscule carotidien. Sem. Hôp. Paris **50**, 854–864 (1974)

Weichert, R. F.: The neural ectodermal origin of the peptide secreting endocrine glands. Amer. J. Med. **49**, 232–241 (1970)

Westbrook, K. C., Guillamondegui, O. M., Medellin, H., Jesse, R. H.: Chemodectomas of the neck. Selective management. Amer. J. Surg. **124**, 760–766 (1972)

Zettergren, L., Lindström, J.: Glomus tympanicum. Its occurrence in man and its relation to middle ear tumors of carotid body type. Acta path. microbiol. scand. **28**, 157–164 (1951)

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