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Benign Nonchromaffin Paragangliomas of the Duodenum

By

HERBERT B. TAYLOR and ELSON B. HELWIG

With 11 Figures in the Text

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A group of unusual polypoid tumors in the periampullary portion of the duodenum have been observed in recent years at the Armed Forces Institute of Pathology. These have not fallen into any of the recognized categories of tumors encountered in this location, although an apparently similar case was reported by DAHL, WAUGH, and DAHLIN, who considered it to be a ganglioneuroma. For reasons to be presented, we believe these tumors are more closely related to benign nonchromaffin paragangliomas than to ganglioneuromas, although the latter designation is still favored, albeit with misgivings, by DAHLIN. Our use of the term "paraganglioma" is in the broader sense of current usage as favored by HAMPERL; LATTES; SMETANA and SCOTT; and others, rather than in the more restrictive sense as originally employed by HOLLINSHEAD and championed more recently by LECOMPTE. This nomenclature seems justifiable from a morphologic standpoint and because in our opinion the similarities between the secretory and chemoreceptor types of paraganglionic structures outweigh the differences. Because of the infrequency with which this tumor is recognized and because of the question that exists regarding histogenesis, the present study was undertaken.

Materials and Methods

Nine examples of duodenal paraganglioma were found among a total of 267 primary and metastatic duodenal tumors on file at the Armed Forces Institute of Pathology. Three cases were contributed from Government hospitals and six from civilian hospitals. Seven tumors were surgical specimens, and two were noted at autopsy. Autopsy observations on the one postoperative death were also available. Clinical summaries were obtained in each case, and additional material was available for special stains. The special techniques used included the Masson's trichome; Snook's reticulum stain; periodic acid-Schiff, both with and without predigestion with diastase; the colloidal iron reaction for acid mucopolysaccharides; mucicarmine; phosphotungstic acid-hematoxylin; Giemsa; the Danielli reaction; the Fontana-Masson argentaffin stain; the azo-coupling argentaffin reaction; Gomori's chromaffin stain; the cresyl echt violet stain for Nissl substance; Bodian's stain for neurites; and both HELLWEG'S and WILLIS' modifications of the Bodian stain. Where wet tissue was available, oil red 0 (ORO) preparations for lipids were made. Parallel studies were performed on a duodenal carcinoid, a duodenal leiomyoma, a functioning adrenal pheochromocytoma, several carotid body tumors, and ganglioneuromas of the coeliac ganglion and of peripheral origin (brachial plexus). Comparison was also made with the material available on five examples of intestinal ganglioneuromas on file at the AFIP.

Since most of the cases were received within the past 3 years, follow-up data are incomplete, but no clinical or anatomic evidence of recurrence or metastasis has appeared in any patient.

Clinical Data. Seven of the nine patients were males. The age at the time of diagnosis ranged from 32 to 72 years, with an average of 51.9 years. Gastrointestinal bleeding, usually in the form of hematemesis and severe enough to require transfusion in all but one patient, was the most frequent clinical manifestation. It was present in six of seven patients on whom this information was available. Four of these patients also complained of epigastric pain described as typical of that of peptic ulcer. Only one patient had anatomic or radiologic evidence of a peptic ulcer, however. The duration of symptoms varied from several weeks to more than 7 years, but information was known in only five instances. Radiographic examination of the upper gastrointestinal tract was carried out in eight of the patients, and a duodenal lesion, usually described as polypoid, was discovered in six.

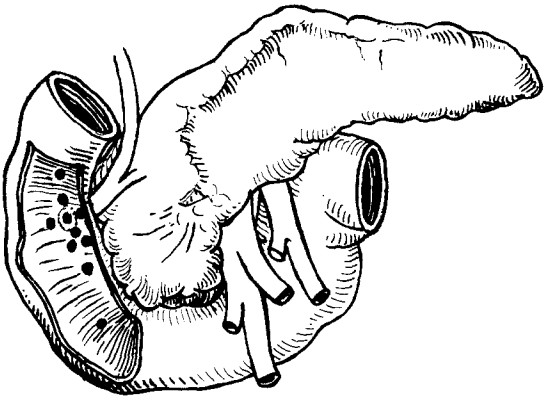

Fig. 1. The location of each of the tumors is indicated by a black dot. The predilection for the region of the papilla of Vater is obvious. (AFIP Neg. 61—2690)

At the time of laparotomy in the patients treated surgically, no other gastrointestinal or intra-abdominal lesions were noted. The three patients on whom autopsies were performed were similarly free of recurrent or metastatic tumor. The cause of death was renal failure secondary to a severe transfusion reaction in one, septicemia complicating cholangitis due to an impacted stone in the common bile duct in one, and bronchogenic carcinoma with metastasis in the third. The latter patient also had a penetrating but apparently fairly recent ulcer in the first portion of the duodenum and superficial erosions of the gastric mucosa, and was the only patient known to have ulceration apart from the tumor. In the patient dying of septicemia, a small intramural nodule in the first part of the duodenum proved to be heterotopic pancreatic tissue, regarded as an incidental unrelated change. No other pertinent lesions were present.

Seven of the lesions were pedunculated, and two were sessile. All were located in the second portion of the duodenum, usually in close proximity to the papilla of Vater (Fig. 1). The diameter of the nodules ranged from 1.0 to 3.0 cm and averaged 1.8 cm. Ulceration of the covering mucosa was noted grossly in five cases, was absent in two, and not recorded as present or absent in two. All lesions were well circumscribed and had a variable but usually firm consistency and a gray to tan homogeneous cut surface that was granular to fibrillar.

Microscopic Examination. Histologically the tumors were similar, being composed of the two cellular elements, one spindle cell and the other epithelioid cell (Fig. 2). The proportion of each constituent varied from almost exclusively epithelioid in two cases to predominantly spindle cell in one case. In general the epithelioid element was the major component. The tumors were both submucosal and within the muscularis but extended to involve the mucosa in six instances (Fig. 3), four of which showed ulceration of the surface. The tumors were in general well circumscribed but not encapsulated (Fig. 4), and where the muscularis was involved the tumor cells infiltrated between the muscle bundles. None of the lesions extended to or beyond the serosa, and no vascular or lymphatic

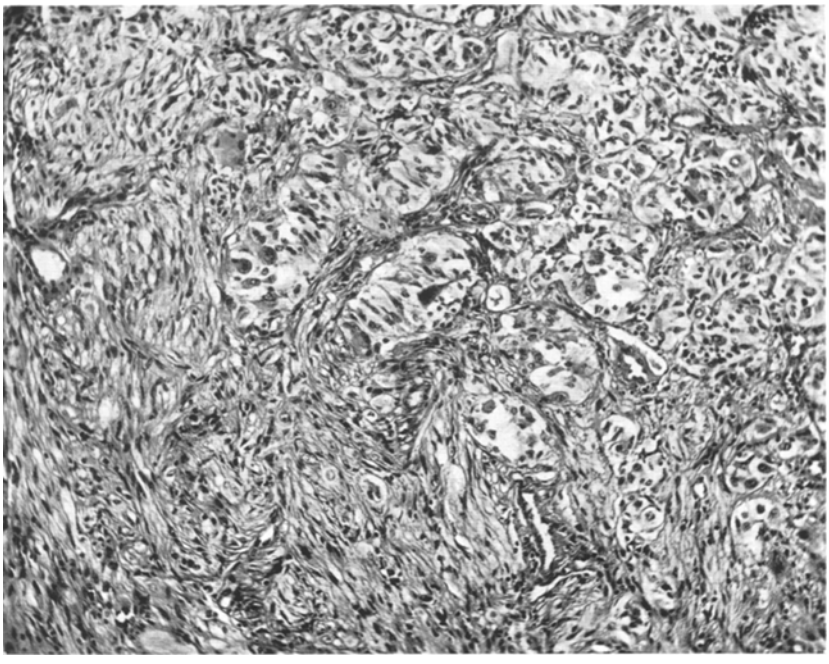

Fig. 2. A typical area showing the combination of spindle-shaped cells and nests of epithelioid cells. Hematoxylin and eosin. Magnification 115 ×. (AFIP Neg. 60—2232)

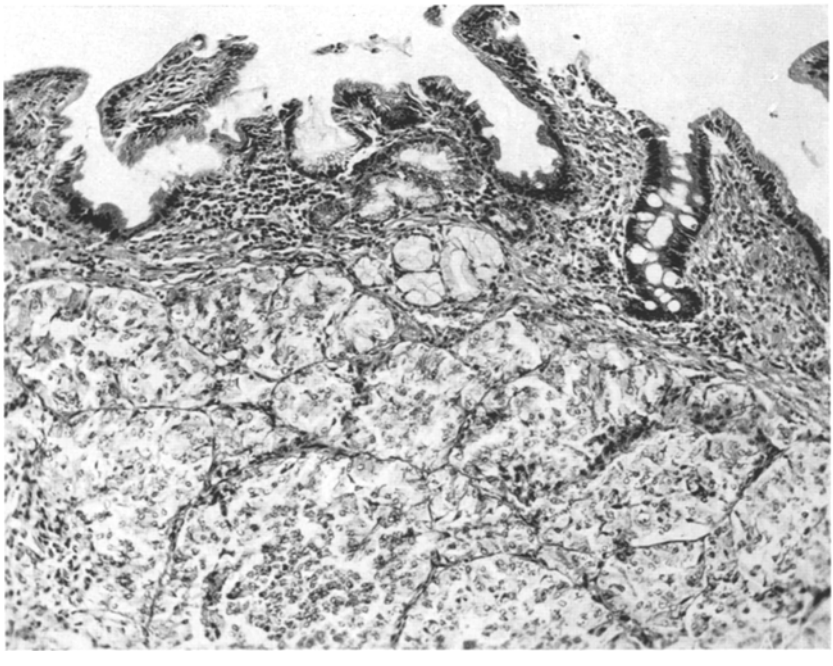

Fig. 3. Extension of the epithelioid component into the stroma of the duodenal mucosa. Hematoxylin and eosin. Magnification 80 ×. (AFIP Neg. 60—6988)

invasion was seen. Mitotic figures were not observed in any case. In a single case a small focus of calcification was present in the tumor, but no other degenerative changes were noted.

Epithelioid Component. This portion of the lesions was comprised of nests of rather large cells ranging from cuboidal to polygonal to oval in shape and having abundant, slightly acidophilic, and finely granular cytoplasm and round nuclei with clumped chromatin content (Figs. 5, 6). These cells were arranged in nests of variable size, with an argyrophilic basement membrane and often a surrounding anastomosing capillary network, resulting in a picture indistinguishable from the Zellballen in carotid body and related tumors (Fig. 7). In some instances these cells were more spindle shaped and oriented radially or in parallel rows (Fig. 8). The epithelioid cells varied to some degree in size, and some had more abundant cytoplasm and large, round nuclei with prominent nucleoli, resembling ganglion cells (Figs. 6, 8), but without any demonstrable axonal elements or Nissl granules. Similar cells were seen rarely in the stromal areas, usually occurring singly. While no Nissl material was found in these cells either, a few had Bodian-positive filaments, usually unipolar (Fig. 9), and these cells presumably were ganglion cells. No vacuoles or other cytoplasmic structures were seen in the epithelioid nests, nor was secretory activity suggested by any of the special stains performed.

Spindle Cell Component. The spindle cell areas were usually less prominent than were the epithelioid nests. These areas were comprised of uniform spindle-shaped cells with ovoid, centrally placed nuclei and amphophilic, nonfilamentous cytoplasm (Fig. 10). There was little tendency for these cells to form fascicles or bundles, although they appeared to flow about the nests of epithelioid cells where the two components were admixed. No myofibrils or collagen fibers were noted in Masson preparations, and the reticulum was scanty and without a characteristic pattern. The cells were morphologically identical to Schwann cells and, except for their lack of organization, were suggestive of the Schwannian component of ganglioneuromas.

Special Stains. Stains for mucins were uniformly negative in the tumors, although the overlying duodenal mucosa reacted normally and served as a built-in control. As noted above, no Nissl substance was found in any of the large ganglion-like cells. Bodian preparations invariably revealed the presence of large numbers of nerve filaments (Fig. 9). They appeared to be an integral part of the lesions and were largely confined to the spindle cell areas and the stroma surrounding the epithelioid nests, although a few appeared to terminate within these groups of cells. The ganglion-like cells seen infrequently in the stroma gave rise to axonal filaments that stained positively, as previously mentioned. No origin of these filaments from the large cells within the glandlike nests was discernible, however.

The modifications of the Bodian technique, in addition to blackening the neural filaments present, also showed that argyrophilic granules were present throughout the cytoplasm of some of the epithelioid cells, which were otherwise morphologically indistinguishable from the non-argentaffin cells (Fig. 11). The number of argyrophilic cells and the intensity of their staining varied from tumor to tumor, but whether the differences in fixation and other factors were responsible

or whether the variability is significant was not apparent. These granules were not evident in Fontana-Masson preparations nor in sections stained by the azo-

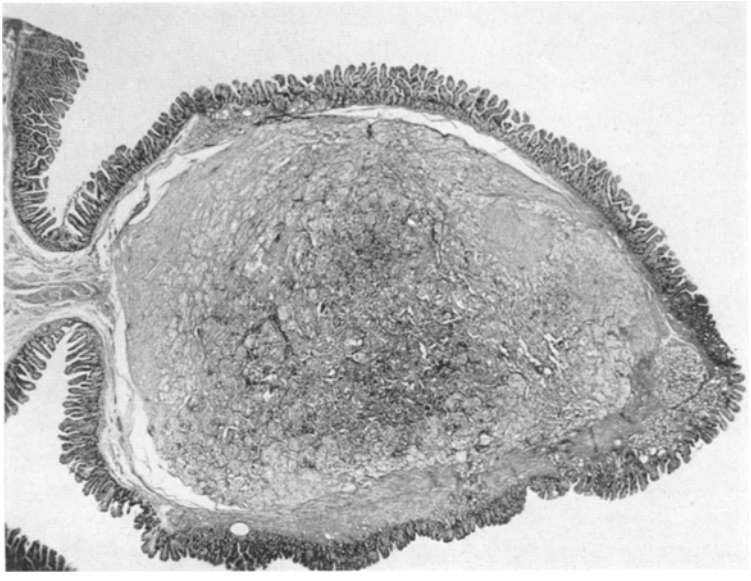

Fig. 4. A low-power view of one of the lesions showing its submucosal location and circumscription. Even at this magnification the dual pattern may be discerned. Hematoxylin and eosin. Magnification 12 ×. (AFIP Neg. 60—2229)

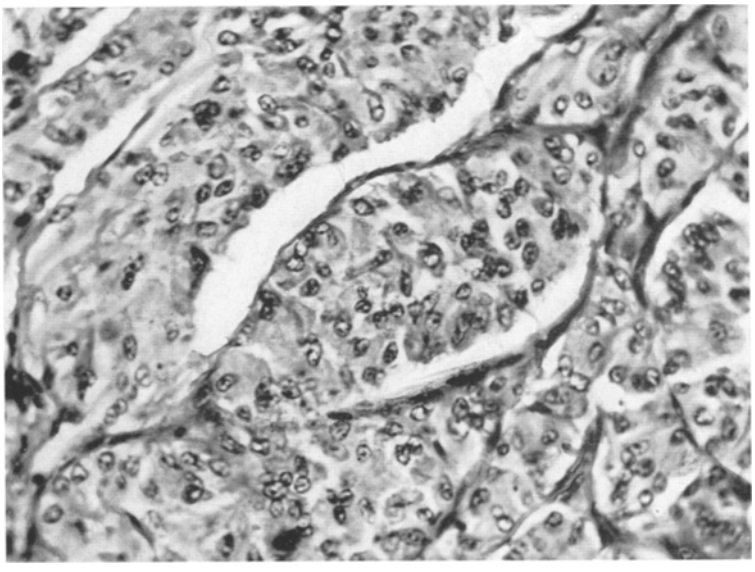

Fig. 5. The epithelioid nests in one of the cases, at higher magnification to show the striking similarity to a carotid body tumor. Hematoxylin and eosin. Magnification 305 ×. (AFIP Neg. 60—6989)

coupling reaction. They appeared identical with the argyrophilic cells described in nonchromaffin paragangliomas by WILLIS and BIRRELL; COSTERO and BARROSO-

MOGUEL; and HAMPERL and LATTES. The Gomori chromaffin stain was negative. Reticulum stains were of value primarily in emphasizing the organoid nestlike

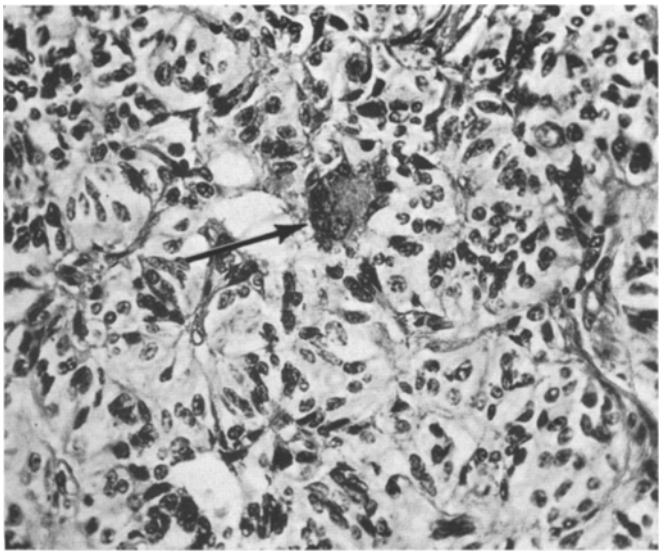

Fig. 6. Epithelioid area in another case. A large cell resembling a ganglion cell is lying adjacent to one of the cell nests (arrow). Hematoxylin and eosin. Magnification 305 ×. (AFIP Neg. 60—2234)

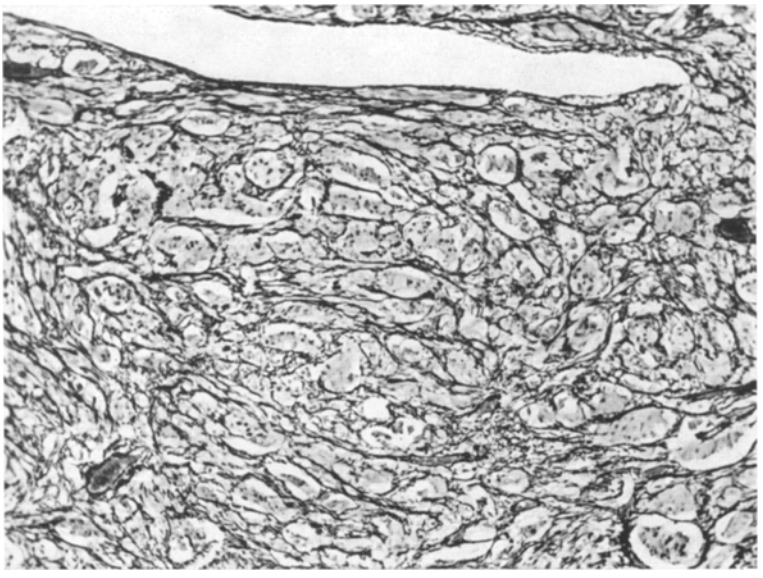

Fig. 7. Reticulum stain of one of the cases to emphasize the alveolar grouping and relationship to the vascular stroma. Snook's reticulum stain. Magnification 80 ×. (AFIP Neg. 60—2238)

grouping of the epithelioid cells and their relationship to the capillary bed that often surrounded them. In the cases where wet tissue was available,

ORO-stained frozen sections demonstrated a faintly positive granularity in the cytoplasm of both epithelioid and spindle cells. The significance, if any, of this

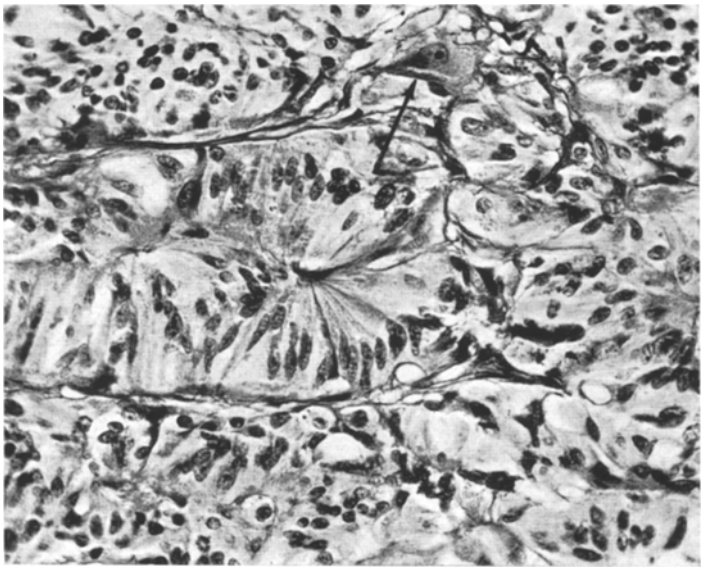

Fig. 8. An epithelioid area showing a radial arrangement of elongated epithelioid cells. A cell resembling a ganglion cell in nuclear detail is also present (arrow). Masson trichrome stain. Magnification 305 ×. (AFIP Neg. 60—2244)

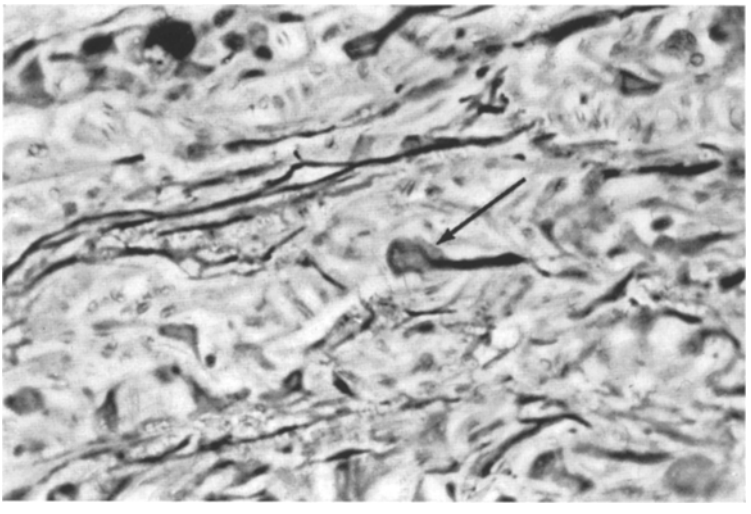

Fig. 9. The presence of neurites and their relationship to the epithelioid nests are evident in this case. A large cell with a unipolar silver-blackened process is also present (arrow) and is presumably a ganglion cell. Bodian stain. Magnification 305 ×. (AFIP Neg. 60—6991)

observation is unknown, but this change was also noted in a carotid body tumor and pheochromocytoma similarly stained.

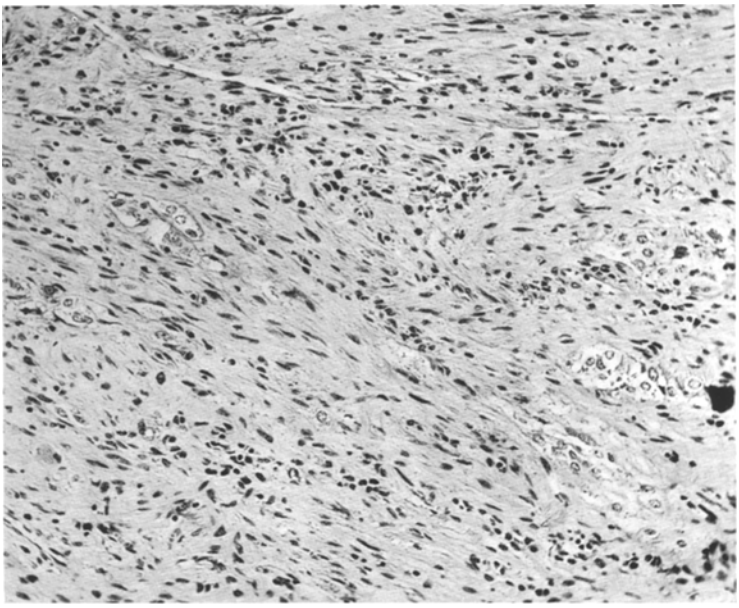

Fig. 10. A case where the spindle cell component predominates. The epithelioid nests are smaller and scattered among the spindle cells. Hematoxylin and eosin. Magnification 115 ×.
(AFIP Neg. 61—2966)

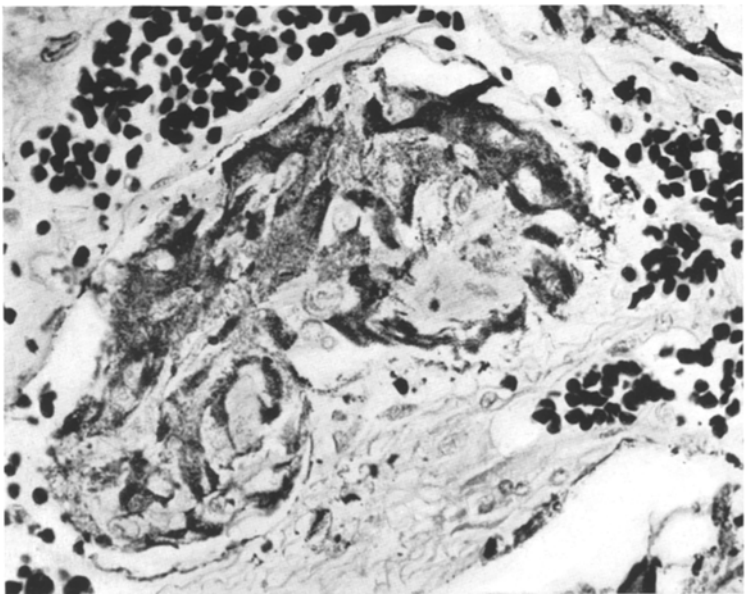

Fig. 11. Argyrophilic cytoplasmic granules within an epithelioid nest are demonstrated in this section stained by Hellweg's modification of the Bodian technique. Magnification 350 ×.
(AFIP Neg. 61—2968)

Discussion

The existence of a problem in classifying these tumors as ganglioneuromas or paragangliomas is not surprising in view of the common origin of the abdominal

sympathetic ganglia and paraganglia (HOLLINSHEAD; SIEGFRIED). Indeed, the derivation of such paraganglia from the embryonic coeliac ganglion suggests that intermediate forms might conceivably be encountered and could give rise to tumors showing all gradations, from a typical ganglioneuroma to typical paraganglioma. The variation in histologic composition in the cases thus far available for study suggests that such may actually be the case in this group of lesions. In our opinion, however, the cases comprising this series would seem best classed as benign nonchromaffin paragangliomas on the basis of the available evidence. The points favoring such a designation are primarily morphologic. The nests of epithelioid cells, often surrounded by a network of capillaries, are indistinguishable from the Zellballen of carotid body tumors and other chemoreceptor structures. This characteristic pattern has not been observed in tumors known to arise from other organs, to the best of our knowledge. Additional support is provided by the modified Bodian preparations, which demonstrated nerve filaments within the tumors lying for the most part in the stromal or spindle cell component surrounding the epithelioid nests and also demonstrated the argyrophilia of some of the epithelioid cells within these nests. Both observations have been described in detailed studies of carotid body and related tumors (COSTERO and BARROSO-MOGUEL; HAMPERL and LATTES; WILLIS and BIRRELL).

The major objection to the term "paraganglioma" that must be met is the absence of any reported paraganglionic structure at the site of origin of the duodenal tumors. A satisfactory explanation is not yet possible, but there is some indirect evidence to suggest that there may in fact be some paraganglionic structures in this location. The existence of abdominal chemoreceptors related to the coeliac and other sympathetic ganglia has been shown in a number of mammalian species. Furthermore, the combination of retroperitoneal tumors in the vicinity of the second portion of the duodenum and typical paragangliomas elsewhere has been documented in the literature (CRAGG). In GOODOF'S patient a carotid body tumor was present as well as a tumor in the head of the pancreas, and ZACKS reported a tumor over the vena cava and right renal vein in a patient who also had a carotid body tumor and a tumor of the glomus jugulare. Finally, the occurrence of paraganglia in this region, although not within the duodenal wall, has been noted in both infant and adult humans by JOHNSON. At the present time a study of serial sections prepared from *en bloc* removal of the tissues from the duodenum to the coeliac ganglion is in progress, in an attempt to demonstrate paraganglionic structures in this location.

The appropriateness of the designation "ganglioneuroma" for these tumors, preferred by DAHL, WAUGH, and DAHLIN, is supported by the presence of a neurofibroma-like stroma in many of the lesions as well as the small numbers of cells that may be ganglion cells. The absence of demonstrable Nissl substance within these cells, however, raises some question as to their ganglionic nature. Furthermore, the presence of ganglion cells in carotid body tumors is an established finding (COSTERO and BARROSO-MOGUEL; WILLIS and BIRRELL). Most important in our opinion is the fact that the epithelioid nests that have been an integral component in all cases in the present series, as well as in DAHL'S case, have not been described in ganglioneuromas of any location, nor have they been observed in material on file at the AFIP. The same objection might be raised with regard

to a spindle cell component in paragangliomas, although just such a constituent was described in nonchromaffin paragangliomas in dogs (JUBB and KENNEDY).

The other diagnostic possibilities that have been raised in these tumors can be excluded with little difficulty. These possibilities have included carcinoid tumor, Brunner's gland adenoma or carcinoma, and islet cell tumors of heterotopic pancreatic tissue. No evidence has been found in our autopsied patients to indicate that the lesions are metastatic. One patient died with carcinoma of the lung, but the tumor in no way resembled the duodenal lesion.

For the above reasons, we prefer to regard this group of neoplasms as benign nonchromaffin paragangliomas. It is acknowledged, however, that additional experience with further cases may shift the balance of the weight of evidence in the opposite direction or lend added support to the possibility that there may be all stages of transition from ganglioneuroma to paraganglioma.

Summary

A series of nine tumors arising in the second portion of the duodenum has been presented. These tumors usually occurred in the fifth and sixth decades and clinically simulated peptic ulcer rather closely. Most of them were polypoid lesions not over 2.0 cm in diameter and were usually demonstrated on x-ray examination of the upper digestive tract. Histologic study invariably showed two elements to be present: one, a spindle cell component similar to the spindle cell portion of ganglioneuromas or neurofibromas; the second, and most often dominant element, nests of epithelioid cells indistinguishable from the Zellballen of nonchromaffin paragangliomas in more typical locations. Modified Bodian stains demonstrated a large number of neurites in the tumors and argyrophilia of many of the epithelioid cells similar to the findings reported in carotid body tumors and other paragangliomas. The histogenesis is considered, and our reasons for regarding these tumors as paragangliomas rather than ganglioneuromas or other suggested lesions are presented.

Zusammenfassung

Auf Grund von neun Beobachtungen werden die makroskopischen und mikroskopischen Befunde der Paragangliome des Duodenums beschrieben. Sie bilden von Schleimhaut überzogene Polypen, die maximal 2 cm Größe erreichen. Sie kommen vorwiegend in der fünften und sechsten Dekade vor. Histologisch setzen sich die Paragangliome aus Spindelzellen einerseits und saftreichen Epitheloidzellen anderseits zusammen. Mit der modifizierten Bodian-Färbung gelingt es, bei einem Teil der letzteren Neuriten nachzuweisen. Viele der saftreichen Epitheloidzellen zeigen auch Argyrophilie. Auf Grund dieser zwei Eigenschaften werden die Geschwülste den Paragangliomen zugeordnet.

References

COSTERO, I., and R. BARROSO-MOGUEL: Structure of the carotid body tumor. Amer. J. Path. **38**, 127—141 (1961).

CRAGG, R. W.: Concurrent tumors of the left carotid body and both Zuckerkandl bodies. Arch. Path. (Chicago) **18**, 635—645 (1934).

DAHL, E. V., J. M. WAUGH, and D. C. DAHLIN: Gastrointestinal ganglioneuromas: Brief review with report of a duodenal ganglioneuroma. Amer. J. Path. **33**, 953—966 (1957).

DAHLIN, D. C.: Personal communication to the authors.
GOODOF, I. I., and C. E. LISCHER: Tumors of the carotid body and of the pancreas. Arch. Path. (Chicago) **35**, 906—911 (1943).
HAMPERL, H., and R. LATTES: A study of the argyrophilia of nonchromaffin paragangliomas and granular cell myoblastomas. Cancer (Philad.) **10**, 408—413 (1957).
HELLWEG, G.: Über die Silberimprägnation der Langerhansschen Inseln mit der Methode von BODIAN. Virchows Arch. path. Anat. **327**, 502—508 (1955).
HOLLINSHEAD, W. H.: Chromaffin tissue and paraganglia. Quart. Rev. Biol. **15**, 156—171 (1940).
JOHNSON, L. C.: Personal communication to the authors.
JUBB, K. V., and P. C. KENNEDY: Tumors of the nonchromaffin paraganglia in dogs. Cancer (Philad.) **10**, 89—99 (1957).
LATTES, R.: Nonchromaffin paraganglioma of ganglion nodosum, carotid body and aortic-arch bodies. Cancer (Philad.) **3**, 667—694 (1950).
LECOMPTE, P. M.: Tumors of the carotid body and related structures (chemoreceptor system). Atlas of Tumor Pathology, Section IV, Fascicle 16, Washington, D. C.: Armed Forces Institute of Pathology, 1951.
SIEGFRIED, J.: Essai d'analyse du plexus solaire (plexus coeliacus), chez l'Homme, d'après son développement. Acta neuroveg. (Wien) **20**, 429—472 (1960).
SMETANA, H. F., and W. F. SCOTT jr.: Malignant tumors of nonchromaffin paraganglia. Milit. Surg. **109**, 330—349 (1951).
WILLIS, A. G.: New methods for staining nerve fibers in pathological material. J. Path. Bact. **68**, 277—283 (1954).
— and J. H. W. BIRRELL: The structure of a carotid body tumor. Acta anat. (Basel) **25**, 220—265 (1955).
ZACKS, S. I.: Chemodectomas arising concurrently in the neck (carotid body), temporal bone (glomus jugulare) and retroperitoneum; report of a case with histochemical observations. Amer. J. Path. **34**, 293—310 (1958).

H. B. TAYLOR,
Armed Forces Institute of Pathology,
Washington 25, D. C./U.S.A.