Paraganglioneuroma of the duodenum: an evolutionary hybrid?

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SUMMARY On light microscopy the neural component of a hybrid neural and endocrine duodenal tumour was characterised by ganglion cells and the endocrine component by epithelioid cells which were both argentaffin and argyrophil. Spindle-shaped cells of indeterminate lineage were also present. Electron microscopy revealed 'pale' and 'dark' cells, the former corresponding to the epithelioid cells and containing many membrane-bound neurosecretory granules, the latter probably corresponding to the spindle cells and containing large numbers of neurofilaments. Occasional cells contained both neurofilaments and secretory granules arranged in a consistent pattern in the cytoplasm. These composite cells may have represented an incompletely differentiated precursor of both the neural and endocrine elements of the tumour.

Eighteen cases of hybrid duodenal tumours containing ganglionic and paraganglionic elements have been described (Dahl et al., 1957; Friesen et al., 1974; Kepes and Zacharias, 1971; Kermarec et al., 1976; Lauzon and Cadotte, 1972; Lukash et al., 1966; Qizilbash, 1973; Taylor and Helwig, 1962; Weitzner, 1970). Two ganglioneuromas of the duodenum have also been reported and a relationship to the hybrid tumour suggested (Gemer and Feuchtwanger, 1966; Goldman, 1968). On light microscopy the tumour exhibits features of both ganglioneuroma and paraganglioma and is composed of diffusely scattered ganglion cells, small solid areas of spindle cells, and epithelial cell aggregates (Zellballen) with peripherally disposed vascular channels. The relative proportion of cell types in each tumour varies but the constitution of the entity is constant. In three of the cases described to date electron microscopy has revealed the presence of 'light' and 'dark' cells, membrane-bound secretory granules of catecholamine type, and fibrils consistent with neurofilaments (Kepes and Zacharias, 1971; Kermarec et al., 1976; Qizilbash, 1973). However, the disposition of secretory granules and neurofilaments within these tumours remains unclear. We report the light and electron microscopic features of a duodenal paraganglioneuroma in an effort to clarify the ultrastructural features of the various cell types and to suggest a possible histogenesis of the tumour.

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Case report

A 65-year-old woman with severe calcific aortic stenosis died in congestive cardiac failure. At necropsy a submucosal mass 1-0 cm in diameter was found on the posterior wall of the second part of the duodenum. The overlying mucosa was intact (Fig. 1a). Bisection of the mass revealed an oval tumour in the submucosa, the cut surface of which had a mottled light brown, haemorrhagic appearance (Fig. 1b).

LIGHT MICROSCOPY

The tumour was circumscribed but unencapsulated and was distinctly demarcated from the duodenal mucosa. Most of it was composed of rounded nests of epithelioid cells surrounded by a delicate network of reticulin fibres and ramifying capillary channels (Fig. 2). The epithelioid cells were exemplified by a large polyhedral cell with a round to oval nucleus which had a smooth nuclear membrane, peripherally condensed chromatin, and a prominent nucleolus. The cytoplasm of the cell was typically plentiful, eosinophilic, and finely granular. Variations in the plane of section resulted in some of the epithelioid Zellballen appearing as regular stacks of elongated cells, as noted previously by Taylor and Helwig (1962) (Fig. 3). Small solid areas of spindle cells with oval nuclei and tapered pale-pink cytoplasm were present, and scattered throughout the tumour were numerous definitive ganglion cells...
Fig. 1  (a) Pedunculated duodenal nodule (arrowed) showing intact overlying mucosa.  (b) Cut surface of nodule with variegated pale, tan, and haemorrhagic areas.  (Actual size  × 2·5)

Fig. 2  Epithelioid cell nests with delicate supporting stroma, resembling Zellballen of carotid body tumour.  (Haematoxylin and eosin  × 400)
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(Fig. 4). The ganglion cells did not appear to bear any constant geographic relationship to the epithelioid cell nests, and although the majority were found between groups of epithelioid cells some were apparently within the Zellballen. In addition to the ganglion cells other neurites were also identified by the Bodian argyrophil stain that had oval vesicular nuclei, prominent nucleoli, and long tail-like processes (Fig. 5). Nissl substance could not be identified in any of the cells by the use of Luxol fast blue/cresyl violet stain. The Bodian stain also revealed large numbers of nerve filaments in the stroma between epithelioid cell nests terminating in bulbous or clublike masses (Fig. 5). At one edge of the tumour a large nerve trunk accompanied by an artery and smaller vessels were identified penetrating the mass. Step sections of the tissue showed progressive branching of the nerve and vessels with smaller twigs pecting out in the fibrovascular stroma between the Zellballen. Masson-Fontana stain revealed large numbers of coarse granules within the cytoplasm in a few of the epithelioid cells. More of these cells, including the argentaffin ones, exhibited finer argyrophilic granules using the modified Bodian technique. Argyrophil granules were also present in some of the ganglion cells.

**ELECTRON MICROSCOPY**

The tissue had been fixed in 10% formol saline. Small blocks were washed in veronal acetate buffer postfixed in 0.1% osmium tetroxide, dehydrated through graded ethanol, and embedded in epon. Sections were cut on an LKB ultramicrotome, stained with uranyl acetate/lead citrate, and examined with a Hitachi HU 12 electron microscope.

The principal feature seen on low-power scanning of the sections was the presence of lightly and darkly stained cells (Figs. 6, 7). The 'pale' cell corresponded to the epithelioid cell of light microscopy and contained large numbers of secretory granules within the cytoplasm. The 'dark' cell appeared to correspond to the spindle-shaped cells of light microscopy and contained numerous fine fibrils resembling neurofilaments, disposed parallel to the long axis of the cell (Fig. 8). Extracellular neurofilaments were not identified. Occasional cells contained both neurofilaments and secretory granules in a regular and characteristic array with a central core of filaments and a peripherally disposed mantle of granules (Fig. 9). In the perikaryon of the ganglion cells neurofilaments and secretory granules were also identified.

The neurosecretory granules described in the three

*Fig. 3 Lamellar arrangement of epithelioid cells within Zellballen in some areas of the tumour. (Haematoxylin and eosin × 250)*
Fig. 4  Binucleate ganglion cell with well-impregnated processes. (Bodian stain × 295)

Fig. 5  Ganglion-like cell with long, well-impregnated tail. Note also nerve filaments with terminal bulbs (arrowed). (Bodian stain × 215)
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Fig. 6 Electron microscopic view of 'light' cell with multiple cytoplasmic granules. (× 9000)
Fig. 7  Electron microscopic view of 'dark' cell. (x 14800)
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Fig. 8 Higher magnification of 'dark' cell showing masses of cytoplasmic fibrils which resemble neurofilaments. Note absence of granules. (× 45 000)
Fig. 9  'Hybrid' cell (arrowed) showing characteristic array of central filaments and peripheral granules. (x 14 800)
cell types above consisted of uniform spherical structures 100-200 nm in diameter with an electron-dense core distinctly separated by a clear halo from a limiting membrane (Fig. 10).

Finally, linear portions of cell bodies which could not be categorised precisely were infrequently seen. These contained secretory granules and prominent membrane-bound, lamellar dense bodies resembling myelin figures (Fig. 11). The latter feature suggests that these are portions of ganglion cells similar to those found in mediastinal ganglioneuromas by Yokoyama et al. (1973). Myelinated nerve fibres were not found.

Discussion

The occurrence of paraganglia in the normal duodenum has not been documented. Pearse and Polak (1971) have demonstrated migration of cells from the neural crest to the duodenal mucosa in experimental animals. Paraganglia are also of neuroectodermal origin. The probability that paraganglia occur in the duodenum is heightened by the occurrence of parangangiomas in the duodenum (see above) and its embryological derivative the gallbladder (Miller et al., 1972). In addition, subserosal paraganglia in the gallbladder have been recorded in three instances (Wolff, 1973); and in the contiguous area of the anterior surface of the head of pancreas Cope et al. (1974) have documented the development of a paranglioma.

Among the 18 cases of duodenal paraganglioneuromas reported to date there is general agreement on the known natural history and morphological
Fig. 11 Cytoplasmic inclusions with prominent lamellated myelin figures and secretory granules (arrowed). (× 21 000)
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Addendum

We have recently seen another such nodule at necropsy in a 69-year-old man. The nodule was in the second part of the duodenum, 1 cm distal to the ampulla of Vater, submucosal in location, and 1 cm in diameter. Light microscopy showed epithelioid Zellballen, solid spindle-cell areas, scattered ganglion cells, and progressive branching of a nerve trunk. The relative proportions of these elements within the tumour differed somewhat from the first tumour described in that there was a larger spindle-cell component and a greater number of ganglion cells. Preliminary examination with the electron microscope showed that this tumour was again made up of two cell types—'pale' cells corresponding to the epithelioid cells and containing abundant secretory granules, and 'dark' cells corresponding to the spindle cells and containing neural-type filaments but without secretory granules. No 'hybrid' cells were seen in the preliminary sections. The nature of the secretory granules is being investigated using immunoperoxidase techniques and this will form the basis of a separate study.