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Extraepithelial intraneural endocrine cells as starting-points for gastrointestinal carcinoids*

Ludwig Auböck and Heinz Höfler

Institute of Pathological Anatomy, Department for Electron Microscopy, University of Graz, A-8036 Graz, Austria

Summary. Endocrine cells can be demonstrated by light- and electron microscopy in the lamina propria of the mucosa of the appendix. They are always in direct contact with a nerve fibre. The endocrine cell (type EC_1 and EC_2 cell) and the polyaxonal non-myelinated nerve fibre are separated from the interstitial connective tissue by a common continous basal lamina. The term "ECC-NF complex" ("EC cell – nerve fibre complex") is suggested by the authors to describe this morphological unit. The intraneural endocrine cells may be derived from neuroendocrine-programmed ectoblasts (Pearse, 1977). The electron microscopic demonstration of these "ECC-NF complexes" in carcinoid tumours of the appendix and of similarly structured "eC-NF complexes" ("endocrine cell-nerve fibre complexes") in carcinoids of the rectum allows us, following the demonstration of small nerve fibres within carcinoids of the appendix, caecum and rectum (and bronchus) to propose a hypothetical parthogenesis of gastrointestinal carcinoid tumours from these intraneural endocrine cells. Carcinoid tumours may develop by proliferation of the intraneural endocrine cells with microcarcinoids as intermediate stages. In this way the histogenesis of the carcinoids is located *a priori* in the subepithelial stroma. Nerve fibres are morphological markers of this proposed mechanism. Assuming a neuroectodermal cytogenesis for the intraneural endocrine cells we therefore also postulate a histogenesis of the carcinoids from the neuroectoderm.

Key words: Extraepithelial endocrine cells – "ECC-NF complex" Ultrastructure – Nerve fibres in carcinoids of appendix – Caecum – Rectum and bronchus – Hypothetical pathogenesis of gastrointestinal carcinoids

Offprint requests to: L. Auböck at the above address

* Dedicated to our teacher Prof. Dr. Max Ratzenhofer on the occasion of his meritorious retirement.

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"Carcinoids are tumours which have their histogenetic origin in disseminated endocrine cells from the entire primitive gut; depending on localization and size of tumour, they show varying degrees of malignancy and endocrine symptoms" (Klöppel and Heitz 1981). The fact that these endocrine cells are found not only within the epithelium of the gastrointestinal tract (Pearse 1969; Solcia et al. 1975a, b and 1979; Grube 1976; Pearse et al. 1977; Mitschke 1977; Dhom 1977; Klöppel and Heitz 1981; Auböck 1982; Borchard 1982), but also in the subepithelial stroma (Masson 1924 and 1932; Ratzenhofer et al. 1969; Soga et al. 1975; Osaka and Kobayashi 1976; Matsuo et al. 1976; Sherman et al. 1979; Ratzenhofer 1981; Stachura et al. 1981; Auböck and Ratzenhofer 1982; Rode et al. 1982; Höfler 1982), has provoked not only a dualistic interpretation of their histogenesis (Ratzenhofer 1982), but is also the basis for discussion in the literature of the following two mechanisms of carcinoid development: 1. The development of gastrointestinal carcinoids from undifferentiated epithelial stem cells (Capella et al. 1973; Soga et al. 1975; Churg and Warnock 1976; Warner and Seo 1979; Isaacson 1981; Lyss et al. 1981). According to this hypothesis, carcinoids develop by proliferation of intraepithelial cells ("tumourlets") and subsequent infiltrative growth into the subepithelial stroma. This mechanism requires demonstration of a connection between tumour cells and epithelial cells. 2. Development of carcinoids from endocrine cells located outside the epithelium in the lamina propria, without connection to the epithelium. Light microscopic demonstration of such extraepithelial endocrine cells within the appendix mucosa was accomplished very early by Masson (1924, 1928, and 1932) and Feyrter (1934). According to Masson's conception, argentaffin endocrine cells were derived from undifferentiated, non-granulated epithelial cells, which migrate in the course of a budding process from Lieberkühn's crypts and enter directly into the subepithelial nerves, differentiating there into argentaffin endocrine cells. Masson considered these endocrine cells within nerve fibres, now isolated from the epithelium, to be the precursor cells of appendiceal carcinoids.

Rode et al. (1982) also find the starting-point for the development of carcinoids in the extraepithelial endocrine cell. Based on our recent light- and electron microscopic findings on extraepithelial endocrine cells in the normal appendix, particularly in neurogenic appendicopathy and on the demonstration of nerve fibres within carcinoids, it is our intention to provide a contribution to the discussion on histogenesis of gastrointestinal carcinoids.

Materials and methods

For light microscopic examination five thousand appendices and two carcinoid tumours of the ileum were fixed in 10% neutral formalin, embedded in paraffin and stained with haematoxilin-eosin. The following stains were used for chosen specimens showing neurogenic appendicopathy, endocrine cells and/or carcinoid: Masson trichrome, silver staining according to Masson-Fontana and Sevier-Munger, sometimes in combination with nuclear fast red or alcian blue staining. Additionally, the ileum, appendix and sometimes the colon from a total of 13 human embryos from the 6th to 16th week of pregnancy were examined.

The material subjected to electron microscopic examination included 50 appendices and 10 carcinoid tumours (appendix, caecum, rectum and bronchus). The material was pre-fixed for 3 h in 3% glutaraldehyde (cacodylate buffer, pH 7,3). After an intermediate soaking in cacodylate buffer, the tissue was post-fixed for 2 h in 1% osmium tetroxide solution and after dehydration in ascending alcohol series it was embedded in Epon 812. Ultrathin sections were contrasted with lead citrate and uranyl acetate solutions. Electron micrographs were made with a Philips EM 200 and EM 400.

Results

Light microscopy

We found endocrine cells in the subepithelial stroma of normal appendices and in neurogenic appendicopathy in every age group. The finding was independent of sex and was evident in embryonic ileum as early as the 8th–15th week of pregnancy. These cells could be demonstrated with Sevier-Munger's silver stain; 80% of them also showed a positive Masson-Fontana reaction. We have chosen the symptom complex of neurogenic appendicopathy as a model for an increase in endocrine cells, as this disease involves a distinct increase in endocrine cells within nerve proliferations in the appendix. In both the normal appendix and in neuroappendicopathy, direct proximity of the endocrine cell to the nerve fibres is mandatory (for review, see "Neurogene Appendikopathie", Höfler 1982). Neither in the embryo nor in the adult we were able to observe a budding of intraepithelial endocrine cells from the epithelial layer in serial sections. In the intramucosal form of neurogenic appendicopathy we regularly saw a proliferation of endocrine cells in the stroma, shown either as an increase in individual cells, or as formation of small clumps (Fig. 1). In two cases of intramucosal neurogenic appendicopathy, we saw microcarcinoids of the appendix within proliferated nerve fibres, far from the appendix epithelium and without any connection to it. Among the 5,000 appendices examined we found 18 advanced carcinoids. There was a combination with neurogenic appendicopathy in 75% of these carcinoids. We did not find, in any of the gastrointestinal carcinoids studied, a connection between carcinoid formation and nerve fibres of the lamina propria. In the submucosa, however, close proximity between carcinoid complexes and larger nerve fibres is very common. Although we never observed a connection between carcinoid complexes and epithelial layers in the early stages of carcinoid development, we have seen a "resorption" of the mucosa by the carcinoid complexes in advanced tumours.

Electron microscopy

Electron microscopic demonstration of "ECC-NF complexes" in the lamina propria of the appendix mucosa. In the appendix mucosa, electron microscopic demonstration of endocrine cells is not limited to the epithelium but, in accordance with the light microscopic findings, is also possible in the lamina propria. Rarely in the normal appendix mucosa and more commonly

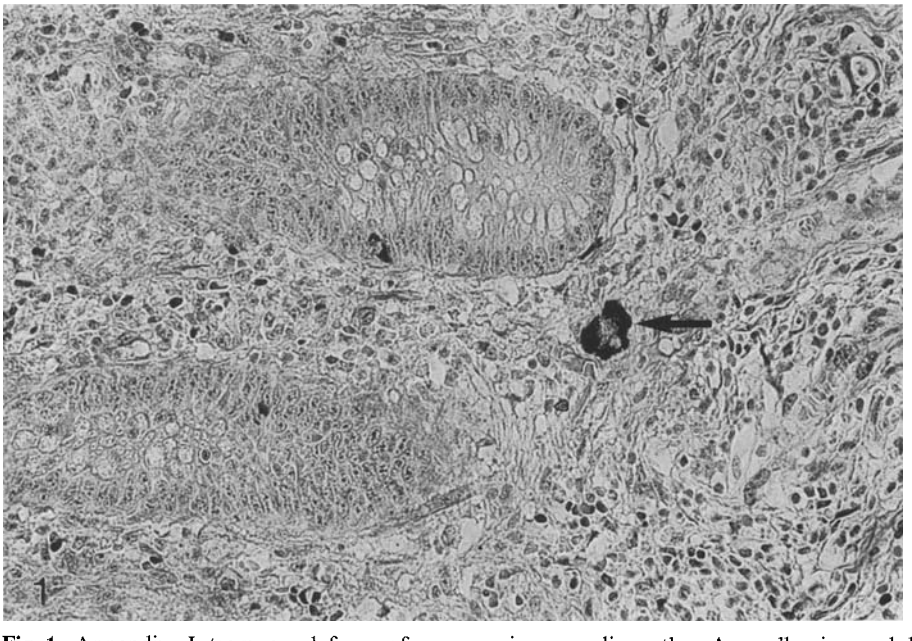

Fig. 1. Appendix. Intramucosal form of neurogenic appendicopathy. A small micronodule with at least five endocrine cells (*arrow*), located in the lamina propria mucosae. Sevier-Munger ×210

in intramucosal neurogenic appendicopathy, isolated extraepithelial endocrine cells may be demonstrated (Fig. 2) at varying distances from the epithelium. In agreement with literature data for the classification of gastrointestinal intraepithelial endocrine cells (Heitz 1977; Solcia et al. 1979), we should like to classify these extraepithelial endocrine cells as EC_1 and EC_2 cells (Fig. 2; for detailed findings see Auböck 1982 and Auböck and Ratzenhofer 1982). What is remarkable about these extraepithelial endocrine cells is not just their location outside the glandular epithelium, but in particular the fact that they are never found as isolated cells in the stroma, but always in closest topographical relationship to a polyaxonal non-myelinated subglandular nerve fibre. This peculiarity led us to call this morphological unit an "ECC-NF complex" ("EC cell – nerve fibre complex", Fig. 2). These complexes are separated from the interstitial connective tissue by a common, continuous basal lamina surrounding both components of the complex. In contrast, the endocrine cell and nerve fibre within the complex are in direct contact via a bimembranous intercellular cleft with no basal lamina. The nerve fibres within the subepithelial complexes in the intramucosal form of the neurogenic appendicopathy are increased, the axons are swollen and show degenerative changes. The intraneural endocrine cells are, however, always free of structural changes. It may be difficult to distinguish clearly the intraneural endocrine cell from the nerve fibre (axon-containing Schwann-cell) when the components of the complex are interwoven (Fig. 2). The relative numerical relationship of the intraneural EC cell to

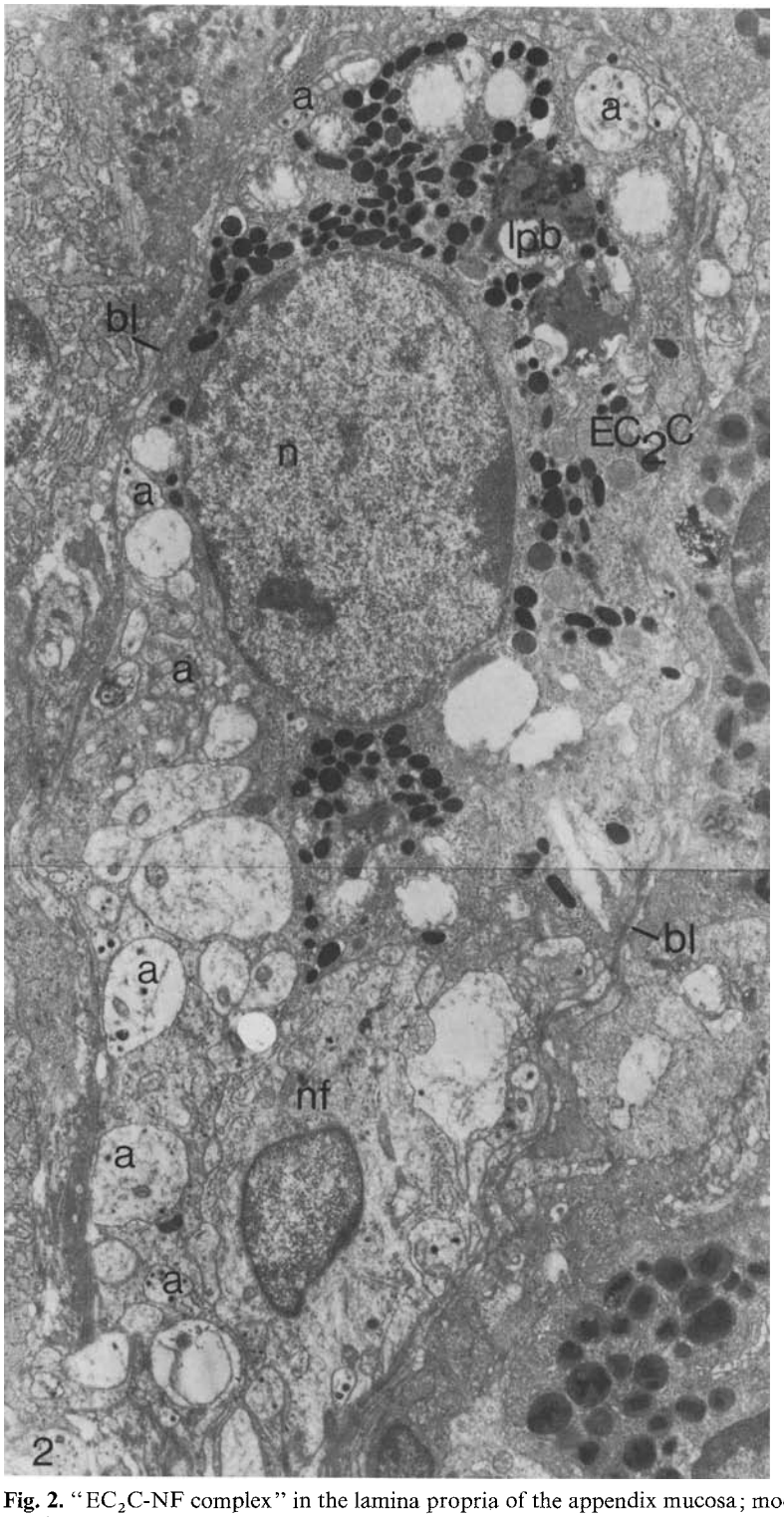

Fig. 2. "EC_2C-NF complex" in the lamina propria of the appendix mucosa; moderately developed neurogenic appendicopathy. The complex consists of an intraneural EC_2 cell (*EC_2C*) with a prominent nucleus (*n*), lipid pigment body (*lpb*), numerous polymorphic electron-dense secretory granules and a non-myelinated nerve fibre (*nf*), whose axons (*a*) are swollen to various degrees. Endocrine cell and nerve fibre are situated within the common basal lamina (*bl*) of the complex. ×11,800

the nerve fibre is 1:1 in the normal appendix mucosa, but can be shifted in favour of the EC cell in intramucosal neurogenic appendicopathy, with up to three EC cells forming a complex with peripheral nerve fibre components (see Auböck 1982, Fig. 15; page 76). The basal lamina surrounding the entire complex emphasizes the nature of this entity as a complex. Such complexes appear in deeper regions of the mucosal stroma and in close vicinity to the cryptal basal lamina. Serial sections revealed no connection with the overlying epithelium. No electron microscopic evidence could be found for a migration of undifferentiated epithelial cells or intraepithelial endocrine cells from the epithelium into the subepithelial stroma.

Electron microscopic demonstration of nerve fibres within carcinoids of appendix, caecum, rectum and bronchus. Analogous complexes made up of EC_2 cell and nerve fibre were found in the stroma between large tumour cell groups of an appendiceal carcinoid (Fig. 3a). The nerve fibre component is usually very small and is always located at the periphery of the complex (Fig. 3a/inset). These "EC_2C-NF complexes" are also shown to be a morphological unit by the surrounding basal lamina which persists intact. Nerve fibres were also found within large tumour cell formations in this appendiceal carcinoid (Fig. 3b, c). These nerve fibres vary considerably in appearance. There are small nerve fibres containing small axons with only a few dense-cored vesicles, neurofilaments or neurotubules enfolded by a remarkably long and twisted mesaxon in light Schwann cell cytoplasm. In addition to these small nerve fibres, there are – though less frequently – also considerably larger, oligoaxonal, non-myelinated nerve fibres within the tumour cell formation (Fig. 4). In the immediate vicinity of these nerve fibres there are often axon-like structures, which are remarkable for their plentiful small, electron-dense granules with longish and round profiles. Nerve fibres are never found deep in the tumour cell area, but are always found immediately below the basal lamina common to the tumour cells and the nerve fibre. There are no indications for penetration of nerve fibres of the interstitial connective tissue into the tumour epithelium.

Demonstration of such complexes was also possible in two out of five carcinoids of the rectum examined in detail by electron microscope. Here, however, instead of intraneural EC cells there were only round-granulated, polypeptide-producing endocrine cells to be found; a fact we would like to express with the modified term "eC-NF complex" ("endocrine cell-nerve fibre complex"). This complex (Fig. 5a) also shows the morphological peculiarity seen in the "ECC-NF complex": there is no basal lamina between the endocrine cell (tumour cell?) and the oligoaxonal Schwann cell, while the bicellular complex as a morphological unit is separated from the interstitial connective tissue of the tumour by a common basal lamina. In both of the rectal carcinoids as well, the electron microscopic "complex" demonstration is not limited to "eC-NF complexes" with an equivalent numerical relationship of the cellular components of 1:1 (Fig. 5a). Rather, such complexes may be found with a considerable shift of the cell relationship in favour of the endocrine cell component. The morphological substrate for

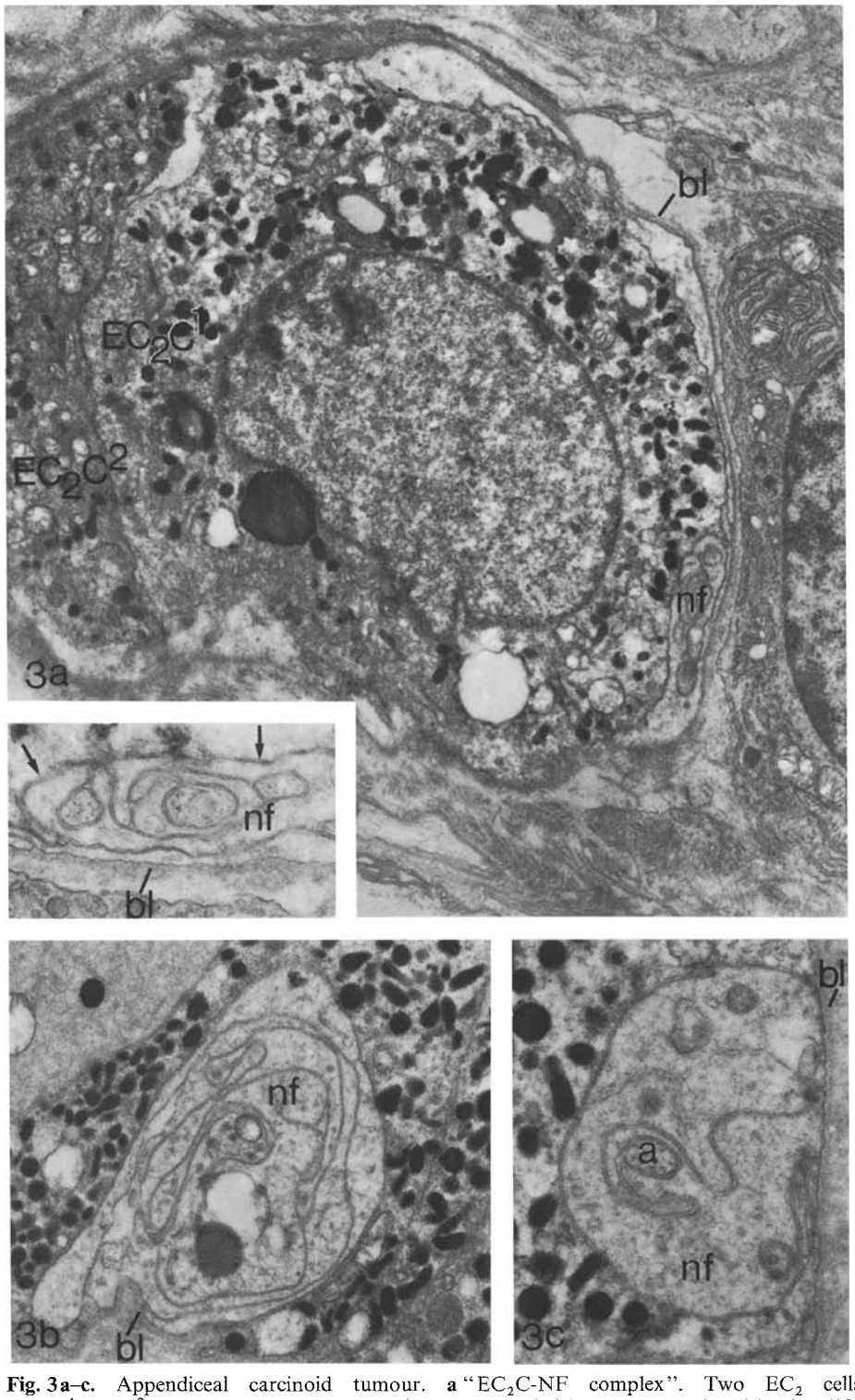

Fig. 3a–c. Appendiceal carcinoid tumour. **a** "EC_2C-NF complex". Two EC_2 cells (EC_2C^1 EC_2C^2) and a small nerve fibre (*nf*) are surrounded by a common basal lamina (*bl*). ×10,800. *Inset:* Nerve fibre (*nf*) with two axons of a serial section of this complex at higher magnification. The border area (↙) between endocrine cell and nerve fibre shows no basal lamina. Basal lamina of the complex (*bl*). ×26,200. **b** Nerve fibre (*nf*) with long mesaxons within the appendiceal carcinoid tumour, directly below the basal lamina (*bl*). ×10,250. **c** Small nerve fibre (*nf*) with only one axon (*a*) on the edge of a large nest of endocrine tumour cells. Basal lamina (*bl*). ×16,100

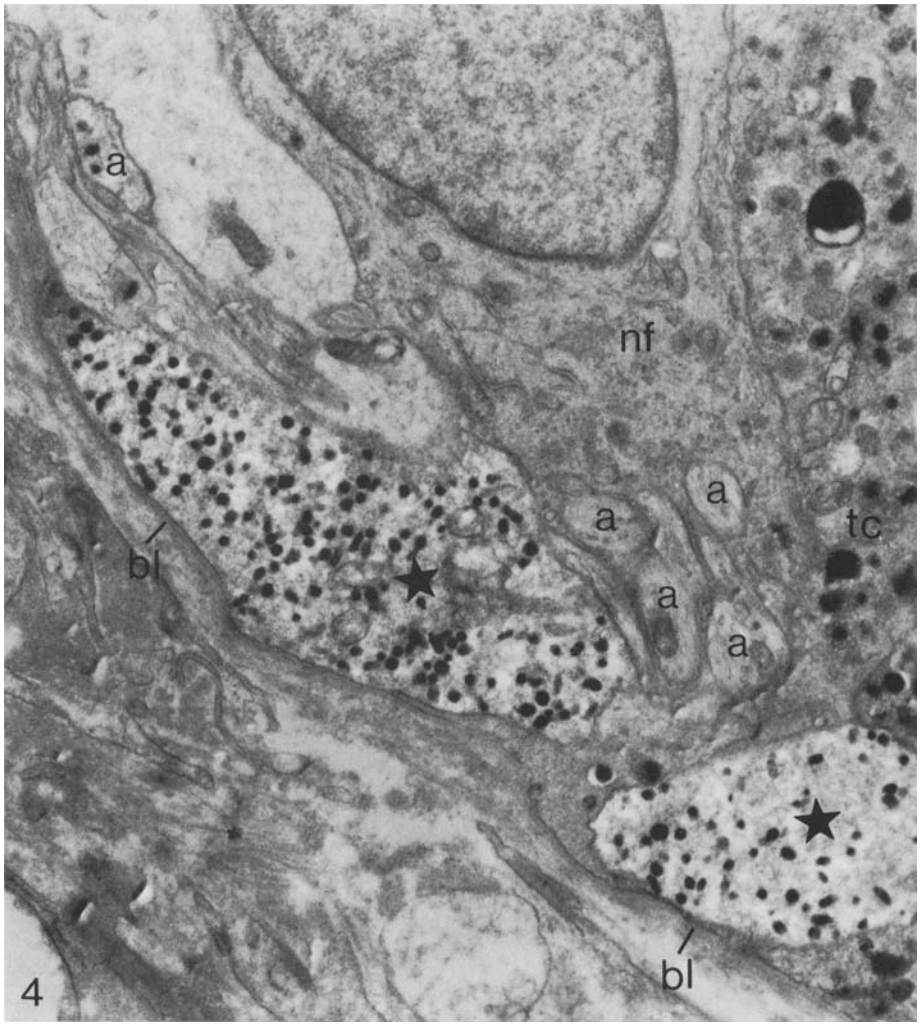

Fig. 4. Carcinoid tumour of the appendix. Large non-myelinated nerve fibre (*nf*) with small axons (*a*) within the appendiceal carcinoid tumour. The nerve fibre is separated from the basal lamina (*bl*) by two axon-like structures (*asterisk*) with numerous small electron-dense granules. Endocrine tumour cell (*tc*). ×12,800

this consists of the medium-sized tumour cell groups containing ten or more endocrine tumour cells and a small intratumourous nerve fibre immediately below the basal lamina (Fig. 5b, c). Upon careful study of the sections, small nerve fibres with varying structure may also be found within large tumour cell formations (Fig. 6a–d). They consist of thin cytoplasmic processes of Schwann cells and a few axons of varying diameter. Small axons contain only neurofilaments and neurotubules (Fig. 6b, d) larger ones also have mitochondria and dense-cored vesicles (Fig. 6a). When axon and endocrine carcinoid tumour cell are in direct contact, however, there are no synaptic membrane structures (Fig. 6c).

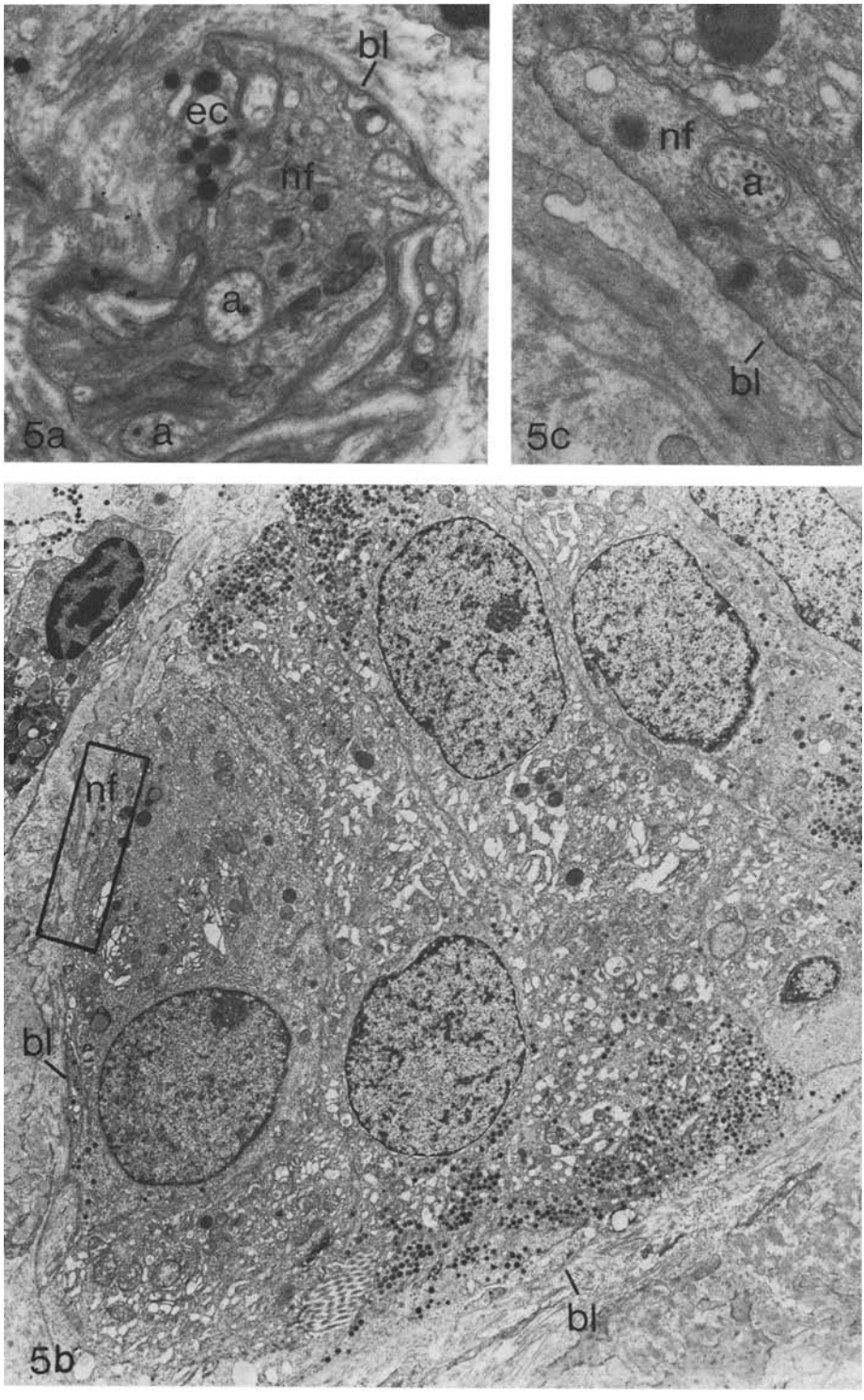

Fig. 5. Carcinoid tumour of the rectum. **a** "eC-NF complex". A round-granulated endocrine cell (*ec*) and a nerve fibre (*nf*) with two axons (*a*) are enclosed by a common basal lamina (*bl*). ×14,100. **b** Medium-sized nest of tumour cells with a small intratumoural nerve fibre (*nf*, ▭), surrounded by a common basal lamina (*bl*). ×7,200. **c** The rectangular area of **b** at higher magnification to show the small nerve fibre (*nf*) with only one small axon (**a**), immediately below the basal lamina (*bl*). ×26,800

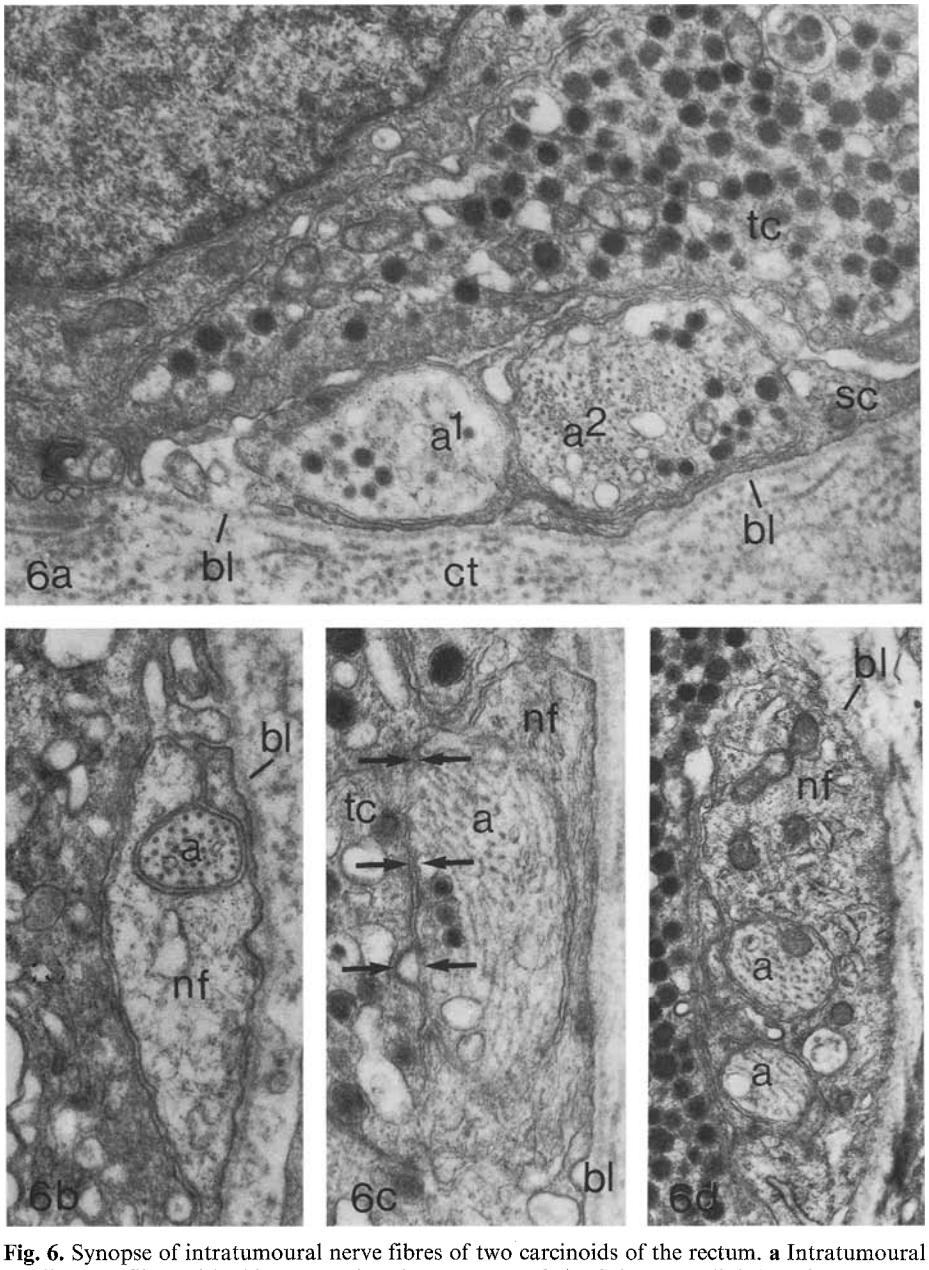

Fig. 6. Synopse of intratumoural nerve fibres of two carcinoids of the rectum. **a** Intratumoural small nerve fibre with thin cytomplasmic processes of the Schwann-cell (*sc*) and two axons (a^1, a^2) with dense-cored vesicles, neurotubules and neurofilaments. Nerve fibre and tumour cell (*tc*) are separated from the connective tissue by a common basal lamina (*bl*). ×16,700. **b** Small intratumoural nerve fibre (*nf*) with one axon (*a*) only. Basal lamina (*bl*). ×15,900. **c** Axon (*a*) of an intratumoural nerve fibre (*nf*) with three dense-cored vesicles. There is no basal lamina (↙) between the axon and the tumour cell (*tc*). Basal lamina (*bl*). ×18,600. **d** Intratumoural nerve fibre (*nf*) with two small axons (*a*). Basal lamina (*bl*). ×16,100

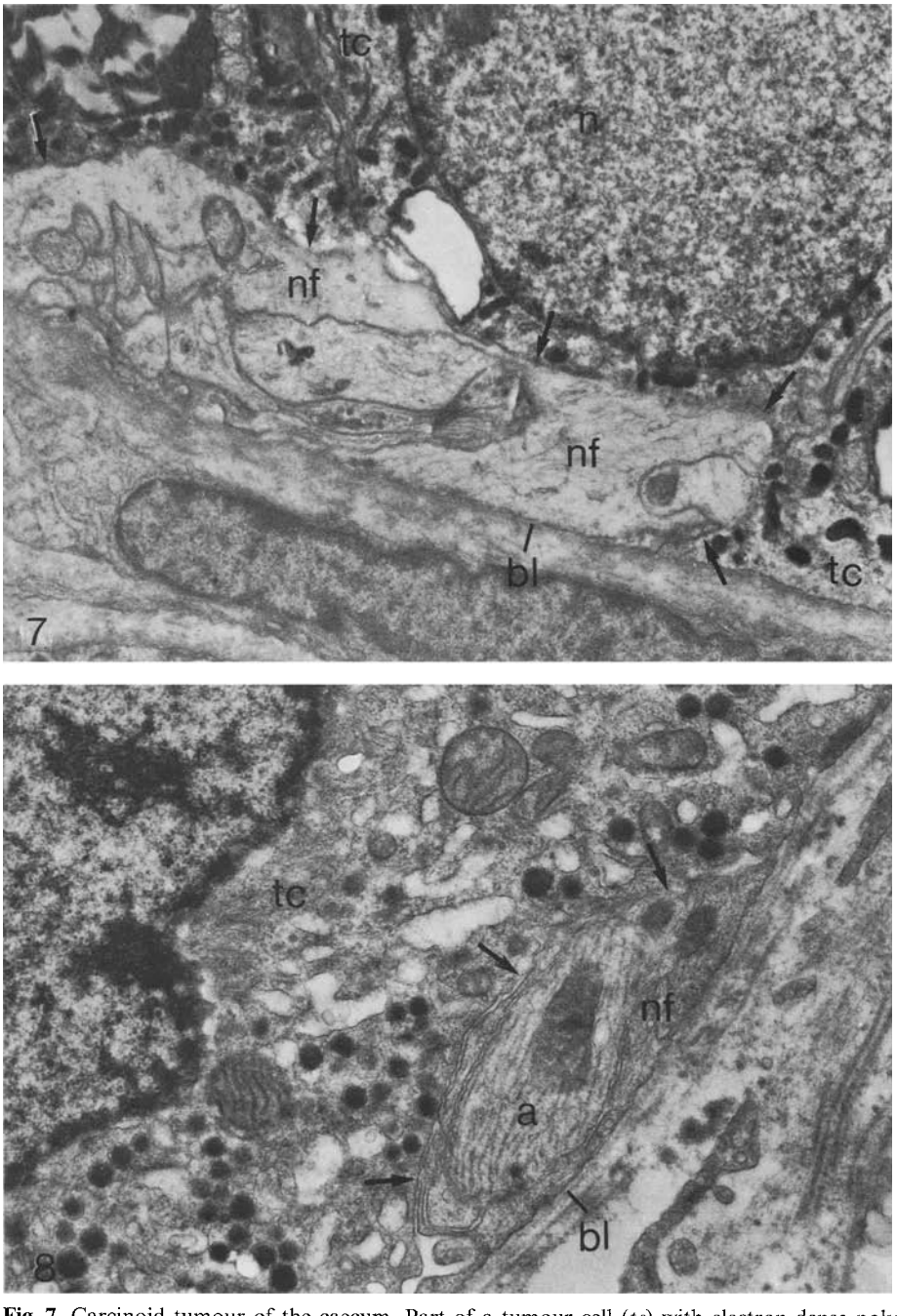

Fig. 7. Carcinoid tumour of the caecum. Part of a tumour cell (*tc*) with electron-dense polymorphic secretory granules and nucleus (*n*). The tumour cell (EC_1 cell type) is in direct contact (↙) with an oligoaxonal nerve fibre (*nf*). Common basal lamina (*bl*) of tumour cell and nerve fibre. × 14,100

Fig. 8. Carcinoid tumour of the bronchus. Endocrine tumour cell (*tc*) in direct contact (↙) with a small nerve fibre (*nf*) with one axon (*a*) only. Basal lamina (*bl*). × 25,200

Small oligo-axonal nerve fibres can also be demonstrated in a carcinoid tumour of the caecum (Fig. 7; for detailed findings see Ratzenhofer et al. 1981). In all investigated gastrointestinal carcinoids the demonstration of such non-myelinated nerve fibres is limited to the periphery of the tumour cell formation. They are always exclusively located immediately below the common basal lamina separating the tumour cells and the nerve fibre from the interstitial connective tissue.

With regard to the existence and the importance of such intratumoural nerve fibres, the electron microscopic demonstration of small nerve fibres within a carcinoid of the bronchus (Fig. 8) seems to be relevant.

Discussion

Masson (1924, 1928 and 1932) and Feyrter (1934 and 1953) provided already very early light microscopic demonstrations of extraepithelial endocrine cells within the appendiceal mucosa. It was a particular accomplishment of Masson to have suggested as early as 1932 the remarkable spatial relationship of these subepithelial endocrine cells to nerve fibres. This topographical relationship can only be seen clearly by the electron microscope: In the normal appendix mucosa and in intramucosal neurogenic appendicopathy the intraneural endocrine cells are always, at least in all the cases we examined by the electron microscope, in direct contact with normal or pathologically altered nerve fibres. Endocrine cell and non-myelinated nerve fibre thus always form a cell complex; the morphological unity of this complex is particularly emphasized by the common basal lamina separating it from the connective tissue (Ratzenhofer et al. 1969; Auböck and Ratzenhofer 1982). According to Masson's concept (1932), these extraepithelial, argentaffine endocrine cells within the appendix mucosa are derived from undifferentiated, non-granulated epithelial cells, which undergo a budding process and migrate from Lieberkühn's crypts into the stroma and settle directly in the subepithelial nerves, where they differentiate to the argentaffine, granulated endocrine cells. Feyrter (1934 and 1953) also proposes a migration of endocrine cells ("endophytia") from the glandular epithelium into the lamina propria. Despite careful light- and electron microscopic studies, we could find no evidence that these budding processes occur pre- or postpartum in appendix mucosa. Rode et al. (1982) mention the lack of this relationship to the epithelium as well. As regards the cytogenesis of the intraneural endocrine cells, we believe – in contrast to Masson and Feyrter – that they develop in loco, i.e. in the mucosal stroma, and are derived from a hypothetical precursor cell, which we propose to call an "endocrinoblast" (Auböck and Ratzenhofer 1982). We thus believe that these extraepithelial endocrine cells probably have their origin in a neuroendocrine-programmed ecto- or epiblast in Pearse's sense (Pearse 1977). These intraneural endocrine cells must therefore be distinguished from the intraepithelial endocrine cells, insofar as the latter, as shown by Andrew (1974), Fontaine and Le Douarin (1977) and Le Douarin (1978), are not of neuroectodermal origin.

Histogenesis of gastrointestinal carcinoids

Our light- and electron microscopic findings and literature data (lit.: see Introduction) indicate that two modes of development are possible for gastrointestinal carcinoids:

1. Development of carcinoids from intestinal epithelial cells. By direct invasion of endocrine cells from the epithelial layer into the bordering stroma and consecutive proliferation (Capella et al. 1973; Soga et al. 1975; Warner and Seo 1979; Isaacson 1981; Lyss et al. 1981). We believe this mode of development to be possible for a particular group of gastrointestinal carcinoids: mixed forms of carcinoma and carcinoid, mucocarcinoids or amphicrine carcinoids may develop in this way (Hernandez and Fernandez 1974; Cooper and Warkel 1978; Abt and Carter 1978; Ratzenhofer and Auböck 1980). We therefore consider these tumours to be derived from the entoderm, but with regard to the secretory products of their endocrine tumour components, they are nontheless to be classified in part as belonging to the APUD system (Pearse 1977).

2. Development of gastrointestinal carcinoids from disseminated extraepithelial, intraneural endocrine cells. In the electron microscopic demonstration of "ECC-NF complexes" and the "eC-NF complexes" and their fine structural characteristics, as well as in the demonstration of the existence of nerve fibres within the gastrointestinal carcinoid tumours examined, we see the possibility of discussing an alternative mode of developmental mechanism for carcinoids. This mechanism of carcinoid development is shown schematically in Fig. 9. Two possible pathological reactions for the "ECC-NF complex" (Fig. 9A and Fig. 2) of the appendix mucosa can be considered: a) A proliferation of the nerve fibre component leads to development of larger complexes consisting of one endocrine cell and a greater number of pathologically altered nerve fibres (Fig. 9B), as a morphological characteristic of the intramucosal form of neurogenic appendicopathy (Ratzenhofer et al. 1969; Auböck 1982; Auböck and Ratzenhofer 1982). b) In addition to the development of neurogenic hyperplasia there can also be an increase in intraneural EC cells. The latter leads to the formation of very small nests of EC cells with small nerve fibre components pushed to the periphery of the complex (Fig. 9C; cf. Auböck 1982, Fig. 15, page 76). The complex character of these cell nests is still preserved by the common basal lamina. These microproliferations are believed to be the morphological substrate for the initial phase of development of the appendiceal carcinoid. In the course of the progressive proliferation of the endocrine cells within these "microcarcinoids", a development of larger nests of carcinoid tumour cells with peripherally situated small nerve fibres (Fig. 9 D and Fig. 3b, c) occur. In our opinion these intratumourous nerve fibres are to be regarded as "morphological markers" of a genesis of larger micronodules from the complex. The developmental mechanism for carcinoids can possibly also

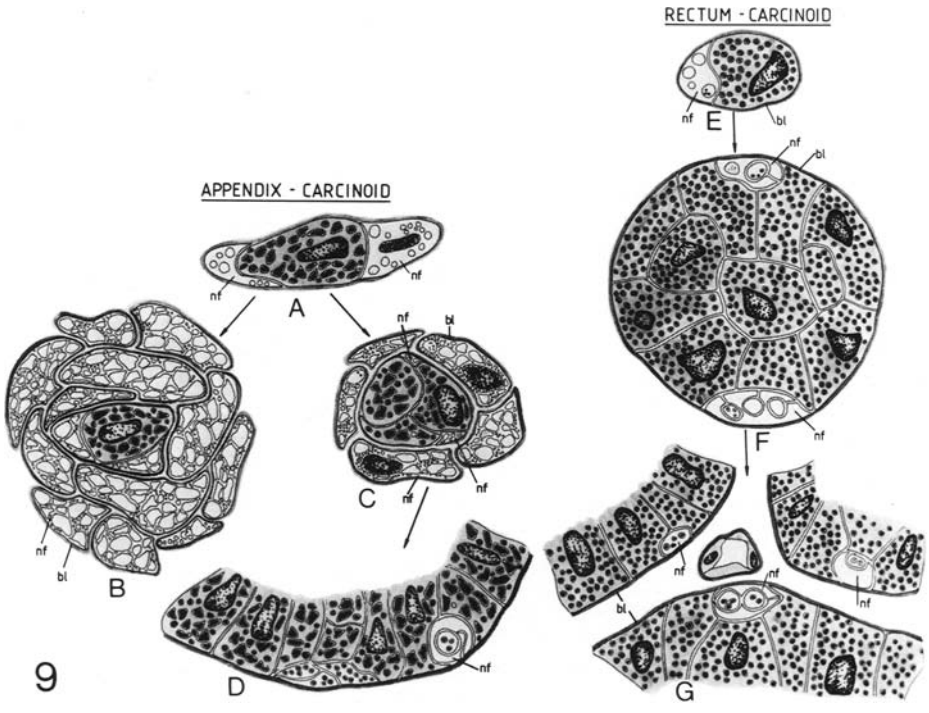

Fig. 9A–G. Schematical description of the hypothetical pathogenesis of carcinoid tumours of appendix and rectum from intraneural endocrine cells. **A** "ECC-NF complex" of the appendix mucosa. **B** Intramucosal form of neurogenic appendicopathy. **C** Neurogenic appendicopathy with a small nest of endocrine cells (microcarcinoid) within the nerve fibre proliferation. **D** Large tumour cell nest of the appendiceal carcinoid tumour with an intratumoural nerve fibre. **E** "eC-NF complex" in the rectal carcinoid. **F** Small nest of carcinoid tumour cells of the rectum with two nerve fibres. **G** Large formation of tumour cells with intratumoural nerve fibres

run its course without phase C. This mode of carcinoid development from the "ECC-NF complex" without simultaneous nerve fibre proliferation seems to be valid not only for the appendiceal carcinoids, but for the 5-HT-carcinoids of the entire intestinal tract as well.

We do not consider the undifferentiated epithelial cells which migrate by "budding" into the nerve fibres as starting point for the development of appendix carcinoids (Masson 1932) but rather believe that carcinoids develop a priori from the "ECC-NF complex" in the subepithelial stroma. We thus contrast with Masson's idea (1932) of an indirect entodermal development of appendiceal carcinoid, the hypothetical consideration of a neuroectodermal genesis from extraepithelial, intraneural endocrine cells. We see a confirmation of this hypothesis on carcinoid development, first presented in Cambridge in 1980 (Auböck et al. 1980), in the light microscopic findings of Rode et al. (1982), where neurosecretory cells of neuroectodermal origin within the appendix mucosa are regarded as precursors of appendiceal carcinoids.

If we substitute an argyrophilic, round-granulated endocrine cell for the argentaffine EC cell in the ECC-NF complex of the appendix, we can also apply the hypothetical considerations on the development of appendiceal carcinoids to the formation of rectal carcinoids. In assuming that the tumour cell areas of varying sizes with intratumourous nerve fibres represent static pictures within the context of a dynamic process of growth, we can also take the "eC-NF complexes" in rectal carcinoids to be the extraepithelial "germ" from which a carcinoid develops (Fig. 9E, F and G). Proliferation of the intraneural endocrine cell through several intermediate stages (microproliferations, Fig. 9F and Fig. 8b) leads ultimately to those large formations of tumour cells (Fig. 9G) within which small, peripheral nerve fibres occasionally still can be demonstrated (Fig. 9G and Fig. 6).

If we relate our electron microscopic findings on nerve fibres within carcinoid tumours of coecum and bronchus to the communications in the literature on the existence of gastrointestinal extraepithelial endocrine cells (stomach: Matsuo et al. 1976; Auböck 1977; Stachura et al. 1981; – small intestine: Osaka and Kobayashi 1976; Sherman et al. 1979; – appendix: Ratzenhofer et al. 1969; Auböck and Ratzenhofer 1982; Rode et al. 1982), the hypothetical developmental mechanism we have presented might also be extended to the development of carcinoids of the caecum and bronchus from adequate extraepithelial endocrine cells. These corresponding intraneural endocrine cells have not yet been demonstrated. The demonstration of their existence will support our hypothetical considerations.

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