The evolution of our concepts on the neural crest-derived cells and their tumors constitutes one of the most fascinating sagas in pathology. The story started in a rather modest fashion, with Kultschitsky detecting a chromaffin cell at the base of the normal crypts of Lieberkühn of the intestine, and Lubarsch and Oberndorfer describing a peculiar little tumor of the small bowel and appendix with the almost apologetic terms of *small carcinoma* and *carcinoid tumor*, respectively. It took the brilliant intuition of Masson to make the link between the two observations through his proposal that carcinoids of the appendix are “endocrine tumors,” and the vision of Feyrter to advance the notion that the isolated cells described by Kultschitsky are part of a vast system of endocrine cells scattered throughout practically all organs endowed with an epithelial lining (his diffuse endocrine or paracrine system).

The saga took a spectacular turn with the observation by A. G. E. Pearse that these cells share important biochemical pathways (symbolized acronimically as APUD) and his daring suggestion that this commonality of biological attributes derives from their common origin from the neural crest, a transient embryonal neural structure already known to be the progenitor of autonomic ganglia and plexuses, paraganglia, and melanocytes. The attractiveness of the theory was weakened by the questionable accuracy of the experimental methods offered in its support and undermined by more rigorous experiments done by other investigators, particularly the ingenious quail-chick chimeric model devised by the French embryologist Nicolle LeDouarin.

These new data led to the abandonment of the neural crest theory and its replacement by the present dogma, according to which neural crest derivates include ganglia, paraganglia, melanocytes, and thyroid C cells, but none of the other neuroendocrine cells (NE) cells, now thought to derive from the same local epithelial stem cells that give rise to all other epithelial cell types of the particular mucosa in which those cells are located. The widely reproduced scheme by Cheng and Leblond provides the best pictorial demonstration of this interpretation as far as the small bowel mucosa is concerned. Predictably, this paradigm switch has led to a substantial change in terminology. Not only terms such as *APUD, APUDoma* and the awkward *neurolophoma* have been expunged from the literature, but the very notions of NE cell and NE tumor have been called into question. While some authors still retain the use of these terms to signify the presence of neural-like phenotypical and biological features regardless of embryologic derivation, others believe that the attribute *neuro* should not apply to cells of endodermal or other non neural derivation, and they refer to these cells as *endocrine tumors*. The pancreas is the best example of this approach, in that no tumor of this organ carries any longer the qualifier *neuro* in the WHO classification of neoplasms of this organ. I think it is fair to conclude that in current scientific language the prefix *neuro* has become objectionable when used in this context. Actually, one could carry this reasoning further by pointing out that legitimate questions are beginning to arise even about the thyroid C cells, the neural crest origin of which had thought to have been validated by the chick-quail model. If the C cell is of neural origin, the question has been asked, how does one explain the immunohistochemical demonstration of thyroid transcription factor-1 (TTF-1), the presence of the thyrotropin receptor gene transcript, and the existence of mixed follicular-C cell and papillary-C cell...
carcinomas?\textsuperscript{14} I trust the reader will recognize in these arguments a reasoning analogous to that which was employed years ago to help debunking the neural origin of endocrine cells and endocrine tumors of the gastrointestinal tract and pancreas.\textsuperscript{7} If we then put a question mark on the neural crest origin of thyroid C cells, the only remaining epithelium-related cell of putative neural crest origin is the melanocyte. This seemed to be firmly established by the already mentioned chimeric experiments of Le Douarin,\textsuperscript{14} the outstanding morphologic studies done by Pierre Masson, and numerous clinico-pathologic observations. One of the latter was the fact that, in contrast to the GI tract, lung and even thyroid, no combined tumors of epithelial cells and melanocytes seemed to exist. If we think specifically of skin and breast, we find that all tumor types combining keratinocytes and melanocytes have been thought to be neoplasms of one or another of these cell types, with a secondary “colonization” by the other cell type.\textsuperscript{2,4,21} This applies to lesions such as Pinkus’ melanoacanthoma, pigmented basal cell carcinomas, pigmented sweat gland tumors, and pigmented breast carcinomas. However, exceptions to this scenario were eventually found. Several authors have reported cases of pigmented breast carcinomas and provided convincing evidence that the tumor contained both neoplastic mammary epithelial cells and melanocytes.\textsuperscript{16,17,23} The same has happened in the skin, in which a few cases of mixed keratinocytic/melanocytic tumors of both basal cell and squamous cell type have been recently described.\textsuperscript{3,8,22} If these cutaneous tumors have indeed a dual keratinocytic-melanocytic component (and not everybody is convinced that this is the case), the neural crest origin of cutaneous melanocytes may also come under attack, as heretical the thought may appear. For one thing, this questioning would vindicate the position of Arthur Allen,\textsuperscript{1} who maintained to the bitter end the belief that melanocytes are, like keratinocytes, ectodermal derivatives.

REFERENCES