The Neural Crest: Its Relations with APUD and Paraneuron Concepts*

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Abstract. The neural crest cells give rise to a large variety of derivatives including neural, mesenchymal, APUD and/or paraneuron cell types.

A better knowledge of these derivatives was partly achieved through studies using LE DOUARIN's quail/chick marker system.

We review here evidences which were thus provided for a neural crest origin of calcitonin containing cells, carotid body, aortic paraganglia, adrenomedulla, and against a neur ectodermal origin of enterogastric and respiratory tract endocrine cells.

The role of neural crest cells in PEARSE's APUD system is discussed. The results implicate that an explanation for the common properties of these cell types and their pathological and biochemical significance should not be looked for in a common embryological origin but at another level.

The place of neural crest and, more generally, neur ectoderm derivatives in the paraneuron concept of FUJITA is examined. The relevance of the epithelial origin of these cell types to their "receptosecretory" function is stressed.

Considering neural crest itself as a unique system is still questioned and discussed here. Its ubiquity and penetration of other systems is pointed out as a widespread phenomenon which is not restricted to APUD and paraneuron systems.

The study of the cells which arise from the neural crest received great impetus with the discovery of a new labelling system (LE DOUARIN, 1969, 1973) which was particularly suitable for this type of work. LE DOUARIN and collaborators then undertook a systemic study of neural crest derivatives casting a new light on this long known and somewhat controversial system (cf. reviews by HÖRSTADIUS, 1950, WESTON, 1970 and LE DOUARIN, 1980). Part of their work dealt with mesectodermal derivatives (LE LIEVRE, 1971, 1978; LE LIEVRE and LE DOUARIN, 1975) which have been reviewed in this journal by NAKAMURA (1982). These studies also clarified the role of the neural crest in the formation of the peripheral nervous system (sensory, sympathetic and parasympathetic) (LE DOUARIN and TEILLET, 1971, 1973) and allowed the discovery of the neural crest origin of several other cell types. Currently known neural crest derivatives are listed in Table 1.

Some time earlier PEARSE (1966) formulated the APUD concept which gathered

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together several cell types. The selection of the APUD cell types was based on common ultrastructural and cytochemical criteria notably the aptitude for uptake and decarboxylation of monoamines precursors after which the APUD acronym was devised. In 1969 Pearse hypothesized that a single origin of these cell types could explain their common properties, some characteristics being possibly retained from a common embryological ancestor by its progeny. The neural crest (and later on, the neur ectoderm, Takor-Takor and Pearse, 1975) was proposed as the most likely single origin for these cell types. This hypothesis was examined in experiments using the quail/chick marker system. The results of these researches will be reviewed in this paper.

Table 1. Neural crest derivatives (in birds)

<table>
<thead>
<tr>
<th>Endocrine system and Paraganglia</th>
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<tr>
<td>Adrenomedullary cells and adrenergic abdominal paraganglia</td>
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<td>Carotid body and thoracic arterial paraganglia</td>
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<tr>
<th>Nervous system</th>
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<tr>
<td><strong>Central</strong></td>
<td>Mesencephalic nucleus of the trigeminal</td>
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<tr>
<td><strong>Peripheral</strong></td>
<td>Sensory neurons in</td>
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<td></td>
<td>Dorsal root ganglia</td>
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<tr>
<td></td>
<td>Superior (IX) and Jugular (X) cranial ganglia</td>
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<tr>
<td></td>
<td>part of the Trigeminal (V) ganglia</td>
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<td></td>
<td>N. B.: Other neurones of cranial ganglia (Trigeminal, Geniculate, Petrous and Nodose) have a placodal origin.</td>
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<tr>
<td></td>
<td>Autonomic neurones in</td>
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<td>Sympathetic ganglia and plexuses</td>
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<td>Parasympathetic ganglia</td>
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<td>Enteric plexuses</td>
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<td>Supporting cells of</td>
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<td>Peripheral nerves</td>
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<td></td>
<td>Dorsal root and cranial ganglia</td>
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<td>Autonomic ganglia</td>
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<th>Pigment cells</th>
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<tr>
<td>Melanocytes in dermis, epidermis and connective tissues</td>
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<td>Melanophores of the iris</td>
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<th>Mesectodermal tissues</th>
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<tbody>
<tr>
<td><strong>Skeleton</strong></td>
<td>Bones and cartilages: facial part of the skull and visceral skeleton.</td>
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<tr>
<td><strong>Connective tissues</strong></td>
<td>Dermis: face and ventral part of the neck</td>
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<tr>
<td></td>
<td>Connective tissues, including adipous cells: face, neck and upper thorax</td>
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<tr>
<td></td>
<td>Connective component of facial and pharyngeal glands: lacrimal, salivary, thyroid, parathyroid, thymic and ultimobranchial</td>
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<tr>
<td></td>
<td>Contribution to the cornea: fibroblasts and endothelium.</td>
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<tr>
<td><strong>Muscles</strong></td>
<td>Musculo-connective wall of arteries derived from aortic arches.</td>
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<tr>
<td></td>
<td>Smooth muscles of the feathers in the face and neck.</td>
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<td></td>
<td>Ciliary muscles</td>
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<td></td>
<td>Contribution to striated muscles in the face, jaw and tongue.</td>
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</table>
In the meantime Fujita (1976, 1977) proposed the concept of paraneurons which share morphological, metabolic and functional features with neurons. Endocrine cells, APUD cells but also sensory cells of various types are included in the paraneuron system. A possible neurectodermal origin of paraneurons had been proposed by Fujita (1976, 1977). He later abandoned this idea and put forward the hypothesis of convergent differentiation of paraneurons from diverse origins (Fujita, 1979). We will include here a statement of the role of the neural crest in the formation of paraneuron cell types.

Some embryological implications of our current knowledge of neural crest differentiation and their relation to APUD and paraneuron concepts will be discussed.

Fig. 1. Construction of a quail/chick chimera by orthotopically transplanting a segment of quail neural primordium into a chick embryo. A. Excision of a rhombencephalic and vagal (cr) neural fragment on a 8-somite chick embryo. B. Isolated quail neural primordium (qr) corresponding to the chick fragment excised in A. C. Dorsal view of the host embryo after the graft. D. This piece of host embryo (as indicated in C) shows a transverse section of the graft and host at the 5th somite level. quail tissue, neural crest area, endoderm, ectoderm, mesencephalic primordium, notochord, 3rd somite.
NEURAL CREST AND DERIVATIVES

The neural crest is a transitory structure which appears early during neurulation. It corresponds to the intermediate territories on top of the neural folds between the dorsolateral ectoderm and the neural tube. Neural crest cells essentially differ, at early stages, from other ectodermal cells by their migrating capabilities. Their early migration has now been described in several species and reinvestigated in the last twenty years using various histological preparations for observation in the light microscope as well as transmission or scanning electron microscope (Weston, 1963; Chibon, 1966; Johnston, 1966; Noden, 1973, 1975; Pratt et al., 1975; Löfberg, 1976; Bancroft and Bellairs, 1976; Waterman, 1976; Derby, 1978; Tosney, 1978; Morris and Thorogood, 1978; Löfberg et al., 1980; Nichols, 1981; Ayer-Le Lievre and Le Douarin, 1982) but the prime cause of this behaviour is not yet known. Due to the early migration and dispersion, in other tissues, of the neural crest cells the study of their derivatives proves difficult and can only be achieved by using an adequate label. The quail/chick nuclear marker system (Le Douarin, 1969) fulfilled all the requirements for a such study, being widespread in every cell type, stable and easy to reveal. It was used in chimeras resulting from interspecific orthotopic grafts of neural primordia (tube and crest). The grafts were done at early stages of embryogenesis (Fig. 1) before the onset of neural crest migration. The migrating cells of the graft (generally quail) could be recognized by the structure of their nuclei compared to the host cells (generally chick) and their differentiation could be followed (Fig. 2).

Fig. 2. Chimeric quail/chick embryo at the 15 somite stage. This section has been made just posterior to the level of the 2nd somite. The quail (Q) neural vagal primordium has been grafted into the chick embryo. Quail neural crest cells (arrows) were migrating under the dorsolateral ectoderm (E). Feulgen and Rossenbeck staining. ×420
Calcitonin containing C cells

*Birds*

Chimeras were prepared by grafting quail rhombencephalic neural primordia in one and a half day chick embryos. When analyzed for chimerism at 3 to 18 days of incubation they revealed that cells from the grafted neural crest made a major

![Image](image.png)

**Fig. 3.** On this ultrathin section of ultimobranchial body of a chimeric embryo (as in Figure 1) an endocrine C cell contains dense core granules in its cytoplasm and possesses a quail nucleus with a large mass of heterochromatin (arrow) $\times 9,000$
contribution to the formation of the embryonic pharyngeal region. They constituted the mesenchyme of this area as well as the musculoconnective wall of large arteries derived from the aortic arches and they were also present in the glands formed from the pharyngeal and branchial epithelia: they penetrated between the thymic lobules, the parathyroid glandular cords and the thyroid follicles where they formed connective strands. They were also mixed with the endodermal cells from the fifth branchial pouch after it had started to disperse on the 9th and 10th days of incubation, and together with them formed the ultimobranchial body (UB) (Le Douarin Le Lievre, 1970).

The differentiation of calcitonin containing cells in the UB of such embryos were evidenced in several ways, 1) by the observation of formol induced fluorescence (Falck, 1962) resulting from the presence of fluorogenic amines, 2) by the presence, at the EM level of electron dense core granules in the cytoplasm of glandular cells of the UB, or 3) by a positive immunocytochemical reaction to anti-calcitonin serum. These three techniques were applied to sections of chimeric UB and combined with histological techniques (Feulgen and Rossenbeck staining, 1924; or electron microscopy) which allowed the distinction between quail and chick nuclei. We could thus show (Le Douarin and Lievre, 1970; Le Louarin et al., 1974; Polak et al., 1974) that calcitonin-containing cells in the bird UB are derived from the neural crest (Fig. 3). Their origin in cells migrating through the embryonic pharyngeal region also provided an explanation for the differentiation of ectopic groups of calcitonin containing cells (Dumont, 1956; Stoeckel and Porte, 1969; Kameda, 1971).

**Table 2.** Different types of explants and presence of C cells in the thyroid gland after 14 days in graft on the CAM of 6-day-old chick embryos.

<table>
<thead>
<tr>
<th>different kinds of explants</th>
<th>stages of operation</th>
<th>results</th>
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<td>17 to 25 S</td>
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<tr>
<td>A</td>
<td>9*</td>
<td>7*</td>
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<tr>
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<tr>
<td>C</td>
<td>17*</td>
<td>39*</td>
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<tr>
<td>D</td>
<td>48*</td>
<td>11*</td>
</tr>
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endoderm □ mesoderm □ number of cases *
The Neural Crest and the APUD and Paraneuron Concepts

Mammals

A somewhat different series of experiments was devised to study the origin of calcitonin-containing cells in mammals.

Mammalian C cells were long considered to be derived from the ultimobranchial endoderm (Godwin, 1937). Indeed this rudiment joins the thyroid and UB cells become distributed between the follicules and sometimes inserted into the follicular epithelium itself (Sato et al., 1966; Pearse and Carvalheira, 1967; Stoeckel and Porte, 1970). Nevertheless, cells with the APUD properties (as defined by Pearse, 1969) which could be C cells' precursors (Pearse and Polak, 1971) had been described in the early mouse embryo in the vicinity of the fourth pharyngeal pouch. Yet no clear proof of the neural crest origin or ultimate fate of these cells was given.

The following four series of experiments were done (Fontaine, 1979) to reinvestigate this question: the thyroid rudiment of 18 to 45 somite mice embryos were dissected and cultured in vivo on chick chorio-allantoic membrane either alone or in association with isolated epithelium and/or mesenchyme of the last pharyngeal pouch (UB rudiment) (Summarized in Table 2). Two criteria were used to identify the C-cells of the graft, 1) their ability to take up L-DOPA and synthesize dopamine, and 2) their ultrastructural features. C cells were not found in thyroid rudiment explants when cultivated alone (series A) but only when the last pharyngeal pouch material was associated with it (series B). The results from the experiments of series C and D indicated that C cell precursors were first present in the mesenchymal component of the fourth branchial arch until the 28 somite stage, after which they started to invade the endoderm of the pouch. This mesenchymal component is known to be of mesectodermal origin (Johnston, 1966). One can therefore infer that the final localization of C cells in the thyroid gland results from a multistep process including first a dorsoventral migration of neural crest cells from the neural primordium to the branchial mesenchyme, second an invasion of the UB endoderm by these cells and finally, the colonisation of the thyroid tissue after inclusion of the UB rudiment in the lateral thyroids. These results supported Pearse's hypothesis of the non-endodermal but neural crest origin of the C cells in mammal embryos as well as in bird embryos.

Carotid body and arterial paraganglia

As previously mentioned, the walls of the arteries forming around the endothelia of aortic arches originate from the neural crest (Le Lievre and Le Douarin, 1973, 1975); the carotid arteries, parts of the systemic aorta, the brachiocephalic trunks and the proximal part of the pulmonary arteries, down to the ductus arteriosus. As early as 7 to 8 days of incubation, cell groups whose origin has long been discussed appear inside the arterial walls or tightly tied to it (Fontaine, 1973). These cell groups form the carotid body, which plays a role as a chemoreceptor, and these paraganglionic masses more or less evenly dispersed in the walls of the arteries. These "arterial paraganglia" are also considered as chemoreceptors or baroreceptors (Kondo, 1974; Ookawara et al., 1974) and would be the equivalent, in birds, of the sinus caroticus in mammals. Two types of cells are found in the glomus, besides nerve fibers and blood vessels. Type I cells contain fluorogenic amines and electron dense core granules in their cytoplasm. Type II cells would appear to play the role of supporting cells for the type I cells, as glial cells for neurons.

In quail/chick chimeras donor cells largely contributed to the formation of the carotid body when the graft was done at the rhombencephalic level. Under these
conditions the whole carotid bodies (except for endothelial cells) were derived from the grafted neural crest; when treated consecutively for FIF and by Feulgen nuclear staining, the cells of the carotid bodies of such chimeras exhibited a bright greenish fluorescence, characteristic of quail type I cells and the heterochromatin rich nucleoli of the quail nuclei (Fig. 4) (Le Douarin et al., 1972; Pearse et al., 1973). The same observation was made for paraganglionic masses in the walls of arteries (Le Lievre and Le Douarin, 1973). Along with the nuclear marker which allowed grafted quail cells to be distinguished from the host chick cells, a cytochemical marker was found: Carotid body type I cells of both species elaborate different fluorogenic monoamines, mainly dopamine and some adrenaline and noradrenaline in quail cells, 5-HT in chick cells (Pearse

Fig. 4. Carotid body of a 14 day old chick embryo which has received at the 10 somite stage a graft of a quail rhombencephalon. a. FIF technique shows a bright greenish fluorescence in the gland. b. The Feulgen and Rossenbeck staining shows that all the fluorescent cells have the quail nuclear marker. ×380
et al., 1973). In chimeric embryos the biochemical differentiation of type I cells corresponded to that of the donor species. Thus catecholamines, instead of indolamine containing cells were evidenced in chick host embryos. This shows that the surrounding tissues do not interfere, in that respect, with the differentiation of graft quail cells in the carotid bodies. At the electron microscope level, type I cells containing small dense core granules, as well as type II cells of the chimeric carotid bodies had the quail nuclear marker indicating that both cell types are derived from the neural crest.

In contrast glandular cords of parathyroid cells are in close space relation to the carotid bodies but they never contained any labeled crest cells; their origin is not neur-rectodermal but endodermal.

**Adrenomedulla and abdominal aortic paraganglia**

Using identical techniques (a combination of FIF and Feulgen and Rossenbeck nuclear staining, transmission electron microscopy) the neural crest origin of adrenomedullary cells which had been proved by other methods (Van Campenhout, 1930; Hammond and Yntema, 1947) was confirmed and even their precise level of origin on the neural axis could be established corresponding to somites 18 to 24 (Le Douarin et Teillet, 1971b; Chevallier, 1972). Adrenaline and noradrenaline secreting cells of the adrenomedulla as well as SIF cells and neurons of aortic and adrenal sympathetic plexuses have the same origin.

**Digestive and respiratory tracts**

Le Douarin and Teillet (1973, 1974) clearly demonstrated that parasympathetic ganglia in organs innervated by the vagus nerve originate in the “vagal” region of the neural primordium.

Particular attention was turned to enteric neural system and gastrointestinal and pancreatic endocrine cells. Auerbach and Meissner’s ganglia as well as the ganglion of Remak (in birds) are derived from the neural crest either from the “vagal” region of the neural axis or, partly, for the posterior abdominal part of the enteric system, from the lumbo-sacral neural crest (Teillet, 1978). In no case, however, were neural crest derived cells found (by these authors or ourselves in similar experiments) in the gut endoderm or as bronchial or gastrointestinal endocrine elements.

However none of the preceding experiments precluded the view that all the cells of neur-rectodermal origin could have migrated in the endodermal germ layer prior to the formation of the neural crest itself. The following experiments were devised to answer this question (Fontaine and Le Douarin, 1977). The endomesoderm of chick embryos was associated with the ectodermal layer of quail blastoderms at presomitic stages 5 to 7 of Hamburger and Hamilton (1952). The recombined embryos were first cultured in vitro for 12 hrs and then grafted on the chick CAM for 14 days to allow a complete histogenesis of the intestinal structures. The latter were analysed with various cytochemical techniques (FIF, silver impregnation) combined with the Feulgen-Rossenbeck staining. In all cases the enteric ganglia originating from the quail ectoderm were observed but in none of the explants were cells of the ectoblast type found in the endodermal epithelium (Fig. 5); in the latter, however enterochromaffin cells differentiated and were evidenced. Thus a neur-rectodermal origin for endocrine cells of the digestive tract epithelium had to be excluded. Similar conclusions were drawn by Andrew (1963, 1974) who isolated from chick embryos, at stage 5 to 14 of Hamburger and Hamilton, the presumptive gut territories or ventral parts of embryos including the gut primordium and grafted them on the chick CAM. Intestinal struc-
tures developed from these aneural explants and contained enterochromaffin cells.

The hypothesis of a possible neuroectodermal origin of endocrine pancreatic cells was also subjected to experimental investigation. The only neural crest cells found in the pancreas originate from the vagal level (somites 1 to 7) of the neural axis (Le Douarin and Teillet, 1973; Andrew, 1976). These neural crest derived cells never had any cytochemical properties of pancreatic endocrine cells, they were dispersed in a few

Fig. 5. Cross section of an intestinal structure which has developed from the association of chick endomesoderm and quail ectoblast. The association was done at stage 7 and the explant was cultured on the CAM for 14 days. The only ectoblastic quail cells were found to differentiate in enteric ganglia, none of them was observed in the epithelium. Feulgen and Rossenbeck staining. ×1,000
and relatively small groups and they were always separated from the two main components of the gland (endocrine and exocrine structures). They differentiated into parasympathetic ganglia, as proved by silver impregnation technique (Fig 6) (Fontaine et al., 1977): Antisera directed against glucagon, insulin and somatostatin were applied to these chimeric pancreases. The endocrine cells so identified never exhibited the quail marker of the grafted neural crest (Fontaine-Perus et al., 1980) indicating that pancreatic endocrine cells do not originate from the neural ectoderm.

Fig. 6. A silver impregnation technique (Ungewitter’s) has been applied to the pancreas of a chimeric embryo (same operation as in Figure 1). The neural crest cells which have migrated in this organ differentiated into nerve cells. This section shows a group of quail cells associated with a large bundle of nerve fibers. ×1,200
Hypophysis and epiphysis

Interspecific grafts of mesencephalic and prosencephalic neural primordia showed that neural crest cells surround the brain rudiment or take part in the formation of meninges and notably reach the Rathke's pouch region (Le Lievre, 1976). They send strands of connective tissue between the pituitary cords of the forming hypophysis but, as yet, have never been seen to differentiate into one of these glandular cell types. Recent studies by Takor-Takor and Pearse (1975) have assigned a neurectodermal origin to the Rathke's pouch itself considering that it is, in fact, derived from the ventral neural ridge.

In the same chimeras, grafted quail cells could be seen forming the epiphysis, pinealocytes and surrounding meningeal tissues both being thus neurectodermal. However, in these experimental conditions, which include the graft of the whole prosencephalomesencephalic neural primordium (neural tube and crest) it was not possible to distinguish between the cells derived from the tube and those from the crest.

NEURAL CREST IN APUD CONCEPT

The first results of Le Douarin's group demonstrated the neural crest origin of carotid body type I cells and calcitonin containing cells of the birds UB and mammals thyroid and confirmed that of the adenomediullary cells. These results gave support to Pearse's hypothesis of a common origin of APUD cell types which was also confirmed for the pituitary cells when the presumed ancestor of APUD cells was considered to be, more generally, the neurectoderm (including neural crest). The neurectodermal origin of some APUD cell types was still to be studied but already a wide interest had been raised in the APUD system and its pathological implications. Indeed Pearse's hypothesis could provide a satisfactory explanation for various malignant conditions such as multiple adenomas syndromes and carcinomas secreting ectopic hormones (Pearse, 1969; Rost et al, 1969; Pearse et al., 1974), assuming that normally unexpressed capabilities of the neurectodermal antecedent could resurge in its progeny cells under particular carcinogenic conditions. The terms "apudomas" or "neurolophomas" and "neurocrispathies" were set as general terms to designate pathological conditions of APUD cells or neural crest derived cells. Yet, in the meantime, further embryological studies showed that several APUD cell types did not share this neurectodermal origin (gastroenteric, pancreatic and bronchial endocrine cells) (cf. Table 3). Thus a common neurectodermal origin could not be put forward to explain the common properties of

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<tr>
<th>Neural crest</th>
<th>Other Ectodermal</th>
<th>Endodermal</th>
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<tr>
<td>Adrenomedulla cells</td>
<td>(**) Adenohypophysis</td>
<td>(*) Parathyroid</td>
</tr>
<tr>
<td>Carotid body cells</td>
<td>(**) Pinealocytes</td>
<td>(*) Pancreatic islets</td>
</tr>
<tr>
<td>Paraganglia</td>
<td>(**) Retina Photoreceptors</td>
<td>(*) Endocrine enterogastric</td>
</tr>
<tr>
<td>Adrenergic Interneurones (PNS)</td>
<td>(*) §</td>
<td>Endocrine bronchial (**)</td>
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<tr>
<td>Calcitonin containing cells</td>
<td>(**) Gustatory taste buds</td>
<td>(*)</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>(**) Hair cells of the inner ear</td>
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<tr>
<td></td>
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<td>Lateral line sense organ</td>
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<td>Merkel cells</td>
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APUD cells. The explanation for coincidences in the normal development and carcinogenesis of APUD cell types could not be looked for in a common embryological ancestor but rather at another level, in the similar biochemical properties of cells from different origins indicating a somewhat convergent development and differentiation.

Moreover the APUD concept renewed FEYRTER’s hypothesis of a diffuse endocrine system integrating the more recent histological and biochemical observations, notably that concerning the polypeptide hormone secreting cells, it emphasized the importance of this APUD group of cells from a developmental, functional and medical point of view thus giving rise to numerous studies in these various fields.

**NEURAL CREST IN PARANEURON CONCEPT**

The paraneuron concept of FUJITA (1976, 1977) is based on a number of common morphological and functional properties. Considering these cells as “receptosecretory,” FUJITA stressed their “neuronal” but at the same time “glandular” features. This system gathers together a large number of cell types (Table 3) including APUD cells; the hypothesis of a common neurectodermal origin of these cell types has been subsequently disproved (FUJITA and KOBAYASHI, 1979).

A number of neural crest derivatives belong to the paraneuron system as previously indicated in this paper. These include the adrenergic interneurones of the autonomic peripheral nervous system (as other ganglionic neurons of the PNS), paraganglia and carotid body cell types, the adrenomedulla (adrenaline and noradrenaline secreting cells) and calcitonin containing cells. Other neural crest derivatives include the melanocytes (cf. HÖRSTADIUS, 1950) The adenohypophysis cells, pinealocytes and retinal photoreceptors are neurectodermal as are the hair cells of the inner ear. In our chimeric embryos, obtained by grafting the mesencephalo-rhombencephalic primordium from quail into chick embryos, there was a participation of grafted cells to the inner ear and otic ganglia, but since these grafts had to be done early, before the onset of neural crest migration, at a stage when the border between presumptive crest cells and otic placode is not clear, some placodal material was included in the graft making it difficult to separate placodal and neural crest derivatives. Nevertheless all cells are neurectodermal in origin.

As for the receptor cells, it is interesting to mention here the work done by SAXOD (1972, 1973) who made duck and chick tissue associations using a marker similar to the quail/chick one. He was able to demonstrate that the sensory corpuscles of Herbst and Gandy in the beak of these birds differentiated from the supporting cells of the peripheral nervous system. Schwann and glial cells of the PNS are derived from the neural crest and further associations of quail and chick tissues directly proved the neurectodermal origin of these sensory corpuscles. Such an origin would also be valid for mechanoreceptors, lateral line sense organs of lower vertebrates and gustatory taste buds. In this latter case we have shown in quail/chick chimeras that the whole mesenchyme of the tongue (and taste buds) is derived from the cephalic neural crest (Le Lievre, 1978).

In contrast we have shown that parathyroid, pancreatic islets, enterogastric or bronchial endocrine cells do not have a neurectodermal origin. Neither do the mast cells which are derived from the endothelial hemangioblasts.

We thus recognize that the neurectoderm makes an important, though not exclusive, contribution to the formation of paraneuron cell types: from the adrenergic interneurones paraganglia or sensory receptors of the peripheral nervous system to the
adrenomedulla, they rather give rise to the more neural part of the paraneuron family.

From the consideration of the origins of paraneuron cell types, as presented in Table 3, it emerges that a common feature of all these cell types is that they are derived from *epithelia* either ectodermal or endodermal. This epithelial origin and its functional significance are even more obvious in more primitive species as coelenterate (Fujiita et al., 1980). In this case the paraneurones retain their ectodermal and endodermal localization. Thus, in the primordial border of the organism with its foreign surrounding, they assume a double function as receptors of information from the external environment and as transmitters of this information by way of a secretion. With the evolution of species, the primitive location of the paraneuron cell types in the epithelia may be lost during the processes of development but their double function as “recepto-secretory” is conserved under various morphological aspects adapted to more complex organisms. This “recepto-secretory” function is stressed as a fundamental property of the paraneurones by Fujiita.

**NEURAL CREST AS A SYSTEM?**

Since its discovery it has appeared difficult to classify the neural crest and its derivatives as members of more general systems. Indeed the existence of mesectodermal derivatives were long controversial mainly as being an exception to the three germ layer theory of Von Baer. The common neural crest origin (or neurectodermal) which was primarily put forward in the APUD and paraneuron hypothesis has also been disproved as discussed in this paper. The neural crest appears first as a unique structure but because it contributes to a large number of tissues, its derivatives do not seem to coincide as a whole with other systems.

The question of a common ancestor for all neural crest cells has been raised. No common ancestral criteria remaining present in its whole lineage as a marker have yet been found. Rather, at least two main cell types have emerged from embryological studies, one “mesectodermal”, the other “neural and related.” The mesectodermal cells seem to be determined early in the neural plate (Nakamura and Ayer-Le Lievre, 1982). Their derivatives are apparently not distinguishable from mesodermal ones and they cooperate in the formation of mixed structures: connective tissues, skeleton (bones and cartilages) and muscles (Le Lievre and Le Douarin, 1975; Le Lievre, 1978; Noden, 1978).

The neural and paraneural derivatives are functionally linked to the nervous system, they constitute its peripheral part and related structures: neurons, supporting cells, some APUD and/or Paraneurones. Beyond its functional significance the unity of this family of neural crest derivatives and its close relationship to the CNS is further proved by a certain plasticity of the differentiation of its members (within the limits of the group) for which evidence has been obtained recently. Thus the differentiation of SIF cells or aminergic neurons has been obtained from the adrenomedullary cells (Olson, 1970; Unsicker et al., 1977, 1978; Olson et al., 1980). By modifying their environment the plasticity of the differentiation of cells of the peripheral nervous system has also been observed. Thus the synthesis of acetylcholine has been evidenced in cultures of neurones of superior cervical ganglia under particular conditions and the influence of specific factors (Furshpan et al., 1976; Johnson et al., 1976; Patterson and Chun, 1977; Ross et al., 1977; Bunge et al., 1978; Patterson, 1978; Johnson et al., 1980; Landis and Patterson, 1981). Conversely the differentiation of adrenomedullary cords or sympathetic ganglia could be obtained from bird cholinergic ganglia (ciliary and
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Remak’s) when grafted in early embryos (Le Douarin et al., 1978). Under the same conditions, sensory ganglionic cells, notably presumptive glial cells, could give rise to adrenomedullary cells and neurones of sympathetic and enteric ganglia (Le Lievre et al., 1980; Ayer-Le Lievre and Le Douarin, 1982). This plasticity makes obvious the high degree of kinship of these cells besides their common origin in the neurectoderm.

Thus it is questionable whether the neural crest itself constitutes a unique or a dual system from the origin. At least two groups of neural crest cells are distinguishable on the basis of their fates. Though some characteristics of the ubiquitous neural crest seem common to all of these cells, namely a late pluripotentiality and a capacity to penetrate various systems: muscular, connective, skeletal but also, neural, paraneuron and APUD, all of them consequently have mixed origins.

These observations stress the importance of convergent differentiations. The mechanisms of this widespread embryological process remains to be elucidated.

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