

# PEDIATRIC ONCOLOGY

editors:

c. raybaud, r. clement,  
g. lebreuil & j. l. bernard

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# PEDIATRIC ONCOLOGY

Proceedings of the XIIIth Meeting of the  
International Society of Pediatric Oncology,  
Marseilles, September 15-19, 1981

*Editors:*

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# Preface

The XIIIth meeting of the International Society of Pediatric Oncology was held at the Children's Hospital, Marseilles, from September 15 to 19, 1981. The meeting was attended by 234 participants – 105 members and 129 guests, representatives of 27 nations.

Unfortunately it was not possible to obtain all the papers presented for publication in these proceedings. Yet the book provides a well-balanced representation of the deliberations.

Part 1 of the book is devoted to tumors of the neural crest, the main theme of the meeting. Following the introductory papers on the mechanisms of migration and differentiation of the neural crest cells and on the genetics of neural crest tumors, many studies on neuroblastoma, covering pathology, clinical features, staging, prognosis and treatment, are presented. It seemed important to us to take stock of our knowledge but also of our ignorance of neuroblastoma, and we hoped to be able to start a cooperative study of the surprising clinical evolution and biological characteristics of this type of tumor.

The other related tumors, which have their origin from the neural crest in common, are much rarer than neuroblastoma and because of this less well known: a re-evaluation of neurofibromatosis, medullary thyroid carcinoma, melanoma and pheochromocytoma is presented here.

Part 2 is devoted mainly to the reports on the trials: SIOP trials on nephroblastoma, medulloblastoma and rhabdomyosarcoma, and the EORTC SIOP trial on osteosarcoma. The management concepts based on the American National Wilms' Tumor Study and several papers concerning this topic are, however, also included.

Part 3 deals with miscellaneous topics such as leukemia and malignant tumors, but an important paper on interim analyses and premature results in clinical trials is also included.

I hope these proceedings will give a good idea of the hard and fascinating work done during this XIIIth meeting, and that they will be useful to all pediatricians and oncologists interested in the treatment of childhood malignancies.

C. Raybaud

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# NEURAL CREST TUMORS



# MECHANISMS OF MIGRATION AND DIFFERENTIATION OF AVIAN NEURAL CREST CELLS

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Morphogenetic processes involve the coordinated events of cell migration, cell proliferation, cell adhesion, cell differentiation and cell death. Analysis of these complex mechanisms by a variety of biological and biochemical techniques is already providing a better understanding of normal embryonic development. These studies are also expected to contribute to the problems of birth defects and cancers.

Through the pioneering works of several embryologists early in this century (1), it became apparent that the neural crest offer an excellent model system to study these integrated mechanisms of organogenesis.

In this paper, we shall review briefly the list of the tissues derived from the neural crest and their level of origin on the neural axis ; then we shall present some recent data on the migratory properties and the differentiation capabilities of the neural crest cells. Finally we will outline possible hypotheses concerning the mechanisms involved in the ontogeny of the peripheral nervous system.

## I THE NEURAL CREST DERIVATIVES AND THEIR LEVEL OF ORIGIN

The neural crest is a transitory structure located at the dorsal border of the closing neural tube. Soon after their dissociation from the neural epithelium, crest cells initiate their migration between the superficial ectoderm and the neural tube. The pattern of migration differs at each axial level and sometimes crest cells traverse long distances before reaching their target sites.

Since crest cells cannot be distinguished from the tissues through which they move, various experimental procedures were devised to follow both their migration and their developmental fate. Early ablation or destruction of the presumptive moving cells, yields uncertain results because of the regulatory capacities of the young embryonic territories (1, 2). As a consequence, the extent of the deficiencies consecutive to the extirpation of a given area of the crest is not necessarily an exact reflection of its normal presumptive fate. In fact, this structure is not sufficiently well delimited and its removal necessitates the ablation of part of the neural tube. Moreover, subsequently the anterior and posterior crest regions left in situ tend to replace the ablated area.

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The use of cell markers under conditions that minimize the disturbance of normal development appears to be the most convenient method of revealing the migration pathways and the fate of crest cells. Isotopic labelling of the nucleus by  $^3\text{H}$  thymidine ( 3, 4) is an accurate and precise method for the study of the early steps of crest cell migration but becomes insufficient when later stages are considered since a rapid proliferation of crest cells dilutes this marker. A permanent marker was found to be associated with quail cell nuclei ; in this avian species, chromatin is highly condensed around the nucleolus, whereas in most other species the heterochromatin is distributed in several small chromocenters ( 5, 6). This difference, particularly evident after DNA staining by the Feulgen-Rossenbeck technique for light microscopy or with uranyl acetate for electron microscopy, is encountered in practically all embryonic and adult cell types. Therefore the behaviour of quail crest cells can be followed in chimaeric chick-quail embryos, when appropriate quail neural tube segments are grafted into chick embryos, as described in fig. 1.

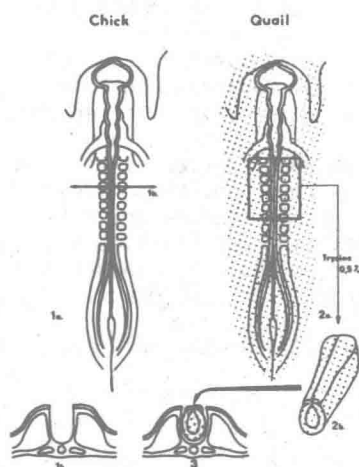


Figure 1. Diagram showing the procedure of isotopic and isochronic grafting of fragments of neural primordium of quail into chick embryos: 1a. Surgical removal of the neural primordium (neural tube + neural folds) in a 9-somite stage chick embryo at the level of somites 1 to 7. 1b. : transverse section at the level of the operation. 2a, b.: enzymatic isolation of the neural primordium taken from a quail embryo at the same stage. 3.: isotopic graft of the quail neural tube into the chick.

Isotopic and isochronic grafts of fragments of the neural primordium (7) or of small areas of the neural fold (8-10) were systematically carried out at all levels of the neural axis.

In the cephalic region, it appears that the neural crest contribution to mesenchymal structures is much more extensive than previously believed. This cell population called "mesectoderm" since Platt (11) contributes to some striated muscles, to cartilage and membrane

bones of the face and of viscera, skeleton, to the dermis of the same region and to the connective tissue of the face, the lower jaw and the tongue. The mesenchymal components of the salivary glands, the thymus, the parathyroid, the thyroid, the pituitary and the muscular and connective tissues of the arteries originating from the aortic arches are also derived from the mesectoderm. The other cephalic crest cells participate in the formation of cranial sensory and parasympathetic ganglia (8, 9, 12, 13).

In the vagal region, crest cells provide most of the parasympathetic enteric innervation (14) ; they also contribute to the ultimobranchial body (Calcitonin-producing cells) and to the Carotid body (type I and type II cells). (15).

In the trunk, crest cells are at the origin of the entire peripheral nervous system and of the paraendocrine cells of the adrenal medulla. All pigment cells with the exception of the retina derive from the neural crest and are found at all levels, not only in the skin but also associated with internal organs.

A list of derivatives along with their level of origin are given in table I.

These studies allowed a fate map for the peripheral nervous system to be established (fig. 2). Interestingly, it was found that crest cells from the level comprised between somites 7 and 28 never penetrate the mesentery ; on the contrary crest cells arising from the level of somites 1-5 penetrated the gut and gave rise to the enteric parasympathetic innervation (14).

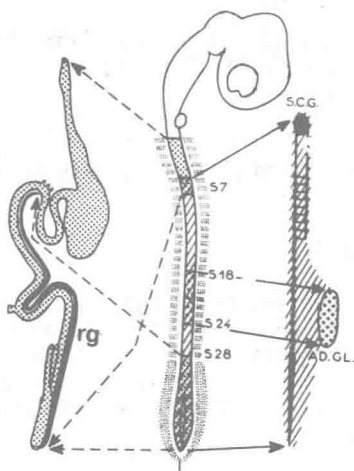


Figure 2. Levels of origin of the trunk peripheral nervous system. The vagal level (from somites 1-7) provides all the enteric ganglia of the preumbilical gut and contributes to the innervation of the postumbilical gut. The lumbosacral level gives rise to the ganglion of Remak and some ganglion cells of the postumbilical gut. The sympathetic chain and plexuses are derived from the entire length of the neural crest posterior to the 5th somite, and the adrenomedullary cells originate from the level of somites 18-24. ADLG, suprarenal gland ; SCG, superior-cervical ganglion ; S, Somite ; rg , ganglion of remak.



## I PERIPHERAL NERVOUS SYSTEM

## A) Cranial Sensory Ganglia

- Trigeminal ganglion (V nerve): anterior rhombencephalon (Rh). Neurons are of a mixed placodal and crest origin.

- Root ganglia : neurons and satellite cells are derived from the neural crest. Facial nerve (VII) root ganglion : mid-Rh, Superior (IX) and Jugular (X) : posterior Rh.

- Trunk ganglia : neurons are derived from ectodermal placodes. Geniculate (VII) : mid-Rh, Petrosus (IX) and Nodulus (X) : posterior Rh.

## B) Spinal Sensory Ganglia : post somite-6

## C) Autonomic ganglia

- Sympathetic ganglia and plexuses : post somite-6

- Parasympathetic ganglia. Ciliary : mesencephalon (Mes), enteric plexuses : somites 1-7 and post somite-28 and Remak ganglion : post somite-28.

## D) Schwann cells of the peripheral nerves

## II ENDOCRINE AND PARAENDOCRINE CELLS

Carotid body type I, II cells : posterior Rh, Calcitonin producing cells : mid and posterior Rh, and adrenal medulla : somites 18-24.

## III PIGMENT CELLS

Melanocytes of epidermis, dermis, mesenteries, internal organs and iris.

## IV MESECTODERMAL DERIVATIVES

## A) Skeleton : bones and cartilage

- Upper jaw : beak, periocular skeleton, maxillary, palate : posterior proencephalon (Pro) and anterior Mes.

- Lower jaw : posterior Mes. + anterior Rh.

- Visceral skeleton = mid and posterior Rh.

## B) Connective tissues

- Dermis, smooth muscles and adipose tissues of the skin.

- Muscles : ciliary : Mes, and striated muscles of face and neck.

- Connective and muscular tissues of the large arteries : Rh.

- Cornea : Pro + anterior Mes.

- Meninges : Pro + anterior Mes.

- Connective components of the pituitary, lacrymal:

Mes. and of the salivary, thyroid, parathyroid glands and the Thymus : Rh.