Original Investigations

Central Neuroblastoma Induced by Transplacental Administration of MethylNitrosourea in Wistar-R Rats
An Electron Microscopic Study

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Summary. Transplacental administration of MNU to pregnant Wistar-R rats at the 16th day of gestation, while inducing cerebral malformations in all the offspring examined, produced only one nervous system tumor. This malignant neoplasm, diagnosed optically as a neuroblastoma, was also examined at the EM level. Although structures strongly suggestive of incipient or abortive synaptic formations were present, well developed synapses were not observed. Among the various neuronal features displayed by the tumor cells, notably some extensive Nissl arrays and numerous subsurface cisternae, several were indicative of maturing nerve cells: branching tumoral processes provided with typical growth cones and dense cored “neurosecretory” vesicles. These vesicles are now considered to be one of the characteristics of newly developing nerve fibers. The presence of these developmental features in a nerve cell tumor helps to substantiate the embryonic origin of neuroblastomas postulated as arising from immature forms and not from de-differentiated cells.

Key words: Neuroblastoma, central — N-methyl-N-nitrosourea — Transplacental carcinogenesis — Neuronal differentiation — Electron microscopy.

N-nitroso compounds, methyl- and ethyl nitrosourea (MNU and ENU) are potent neurotropic carcinogens capable of inducing tumors in organs remote from the inoculation site. After chronic oral or parenteral administration they produce tumors of the central and peripheral nervous systems selectively, the central neoplasms being exceedingly gliomatous except for rare instances of sarcomas and gangliocytomas (Stroobandt and Brucher, 1968). The IV or SC injection of ENU into pregnant rats resulted similarly in multiple neurogenic neoplasms of the offspring after a latency period of 5 months or more (Kleihues et al., 1968). When transplacentally administered both substances also demonstrate a teratogenic effect whose mechanism has been considered alternatively similar to (v. Kreybig, 1970) or different from (Ivankovic and Druekrey, 1968) the oncogenic one.

These results prompted us to utilize MNU for transplacental tumor induction in rats. While we succeeded in the production of numerous cerebral malformations, only a single nervous system tumor was induced: an intraspinal neoplasm which was optically diagnosed as a neuroblastoma. This association between powerful teratogenic effects and the production of a nerve cell tumor serves to reinforce the concept of anomalous development thought to underly the genesis of central neuroblastomas (Willis, 1963).

Central neuroblastoma, a very rare tumor entity, is classified among the “primitive neuroepithelial tumors” which are thought to be derived from the earliest stages of neural cytogenesis because of their uniform cytological appearance (Fujita, 1958; Fujita, 1965; Rubinstein, 1970). In addition, a propensity to mature and to undergo conversion into more benign forms has been postulated for their whole group (Deck, 1969; Rubinstein, 1972). It is indeed in both central (Kernohan et al., 1932) and peripheral (Wilkerson et al., 1967) neuroblastomas that occur the most frequently reported examples of spontaneous cure, regression or maturation in neoplastic diseases. Thus in regard to their biological behavior the so-called embryonal tumors stand out when compared with the more usual gliomas, both human and experimental, where a strong tendency towards anaplastic growth is observed (Wechsler et al., 1969).

It is on the basis of these present day concepts of tumor cytogenesis that an ultrastructural study of the experimental neuroblastoma was performed. After verifying the neuronal origin, attempts were made to compare some peculiar submicroscopic features with the maturation process of nerve cells in vivo or in vitro.

Material and Methods

A single oral dose of MNU (5 mg/kg b.w.) was given to 5 pregnant Wistar-R rats on the 16th day of gestation. The 15 surviving offspring were sacrificed between