Pediatric and Developmental Pathology 8, 305–306, 2005
DOI: 10.1007/s10024-005-2162-5

In Situ Neuroblastoma: An Important Concept Related to the Natural History of Neural Crest Tumors

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Received February 7, 2005; accepted February 7, 2005; published online July 8, 2005.

ABSTRACT

Since the initial description of the entity known as "*in situ* neuroblastoma," thoughts about the origin, fate, and clinical significance of this anatomic finding have influenced the field of neuroectodermal tumor biology. This paper discusses the importance of the original description of *in situ* neuroblastoma and how the entity fits into contemporary models of neuroblastoma heterogeneity.

Key words: neuroblastoma, *in situ*, heterogeneity, regression, cell rest

In 1963, the concept of *in situ* neuroblastoma was first proposed by Beckwith and Perrin [1]. This is one of the best examples of a unique idea that was developed from meticulous studies of archival autopsy materials. They summarized and defined *in situ* neuroblastoma as an adrenal lesion of microscopic size that is cytologically identical to typical neuroblastoma and is detected in infants without demonstrable metastases. They collected a total of 13 cases from the autopsy files at Los Angeles Childrens Hospital, Cincinnati Children's Hospital, and the Cincinnati General Hospital. Incidences of *in situ* neuroblastoma in their report were 1 of 249 infants younger than 3 months (Los Angeles Childrens Hospital series) and 1 of 179 infants younger than 3 months (Cincinnati Children's Hospital series), respectively. As indicated by their own calculation, however, the frequency of *in situ* neuroblastoma was 40 to 50 times the expected incidence of primary adrenal neuroblastoma in children before the age of 16 years.

Subsequently, several investigators reported their own experience with similarly high frequencies, and some of them started questioning the neoplastic potential of *in situ* neuroblastoma [2–6]. To date, no one has yet demonstrated a clonal proliferation of genetically abnormal cells in this unique adrenal lesion. In their original article, Beckwith and Perrin offered the most tenable hypothesis that "only a small portion of *in situ* neuroblastomas ever become clinically apparent [and] the majority of such lesions actually disappear ..." [1]. It is also interesting to note that in the birth cohort in Quebec, Canada, during the period when the mass screening program took place by determining urinary VMA (Vanillylmandelic Acid) and HVA (Homovanillic Acid) levels at the age of 3 weeks and 6 months, the incidence of neuroblastoma cases increased 2- to 3-fold without any significant decrease in the population-based mortality [7,8]. When the observations of Beckwith, Perrin, and others and data from the Quebec project are combined, it seems that many *in situ* neuroblastomas do not make themselves detectable even by preclinical screening.

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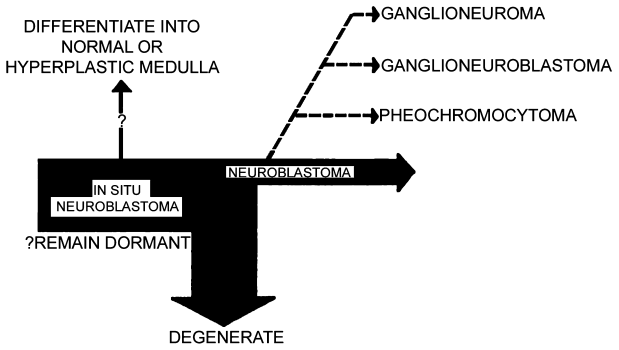

Figure 1. Original figure from Beckwith and Perrin, 1963 [1]. The original legend read: ''The possible fates of *in situ* neuroblastomas. The leading theoretical possibilities are shown. Dotted lines are used to indicate the maturation of neuroblastomas into more highly differentiated neoplasms. This theory is supported by a considerable body of evidence, but has not yet been conclusively proven.'' Reprinted from Am J Pathol 1963;43:1089–1104, with permission from the American Society for Investigative Pathology.

One of the most insightful points in the original Beckwith and Perrin article was found in their Figure 1, which illustrated the possible fate of *in situ* neuroblastoma. They speculated a natural history of peripheral neuroblastic tumors (pNTs; neuroblastoma, ganglioneuroblastoma, ganglioneuroma) that might include involution (regression) and maturation [1]. This concept has been adopted and incorporated in the International Neuroblastoma Pathology Classification that distinguishes a favorable histology group from an unfavorable histology group of pNTs [9]. According to the International Neuroblastoma Pathology Classification those neuroblastic tumors/lesions in the favorable histology group are in the process of involution/regression or within the age-linked framework of maturation. In retrospect all of the photomicrographs of *in situ* neuroblastomas shown in the Beckwith and Perrin article [1], whether they were neoplastic or nonneoplastic (or "cell rests"), had the morphologic characteristics of favorable histology group.

Most importantly, Beckwith and Perrin clearly prophesized the direction of future neuroblastoma research in their article by stating that "certainly from the standpoint of their clinical behavior, tumors grouped under the term 'neuroblastoma' because of histologic similarities are biologically a very heterogeneous group. Elucidation of the nature and causes of this heterogeneity should constitute a major advance in our effort to control neuroblastomas" [1]. More than 40 years after publication, this prediction has been fulfilled. Molecular genetic studies have confirmed the heterogeneity of pNTs, and analysis of the biological properties of individual cases has become a cornerstone of contemporary prognostic algorithms and treatment protocols [10]. We still have much to learn about controlling neuroblastomas, but meaningful progress continues to be made by recognizing and investigating their biological heterogeneity. This legacy of Beckwith and Perrin's classic paper reminds us that huge insights can arise from creative thoughts about even the smallest lesion.

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