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**ADVANCES IN
NEUROBLASTOMA
RESEARCH 4**

Editors: Audrey E. Evans
June L. Biedler
Garrett M. Brodeur
Giulio J. D'Angio
Akira Nakagawara

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ADVANCES IN NEUROBLASTOMA RESEARCH 4

Proceedings of the Sixth Symposium on Advances in Neuroblastoma
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Preface

The Children's Hospital of Philadelphia has hosted an international conference devoted to neuroblastoma research every three or four years since 1975. The first one, held in a small conference room, was attended mostly by pediatric oncologists, a few pathologists, and a sprinkling of geneticists. The most recent one, in 1993, was the sixth such conference. It was attended by over 200 people from all over the world, with a large proportion of molecular biologists and other basic scientists interested in this tantalizing neoplasm. The focus of the 1993 symposium, held over three days, was on laboratory studies as they relate to neuroblastoma. The first day was devoted to Genetics, the second to Differentiation, and the third to Therapy and Screening.

This volume contains the manuscripts of the verbal presentations and transcripts of the discussions, as well as the posters that were displayed.

At the 1990 conference, many of the papers in the genetics session dealt with *N-myc* amplification and its relationship to aggressive behavior. It is increasingly apparent that this is only one of the changes that lead to aggressive disease; there are other equally aggressive tumors that lack obvious gene amplification. Many of the papers in the 1993 genetics session dealt with a possible suppressor gene in the region of 1p36, and its deletion in a subset of tumors. A study of tumor specimens from high-risk patients showed that *N-myc* amplification and 1p loss of heterozygosity (LOH) were associated strongly with each other and with a bad outcome. Nevertheless, in half the patients, neither *N-myc* amplification nor 1p LOH was detected. A similar study, which included patients with both good and bad prognoses, showed that only one out of 12 patients with low-stage disease had 1p LOH and none had *N-myc* amplification. In contrast, one-third of the more advanced patients had 1p LOH, *N-myc* amplification, or both. A new area of research involved expression of the *MDR1* gene. *MDR1* expression occurred with the same frequency in localized or metastatic disease, but was associated with an increased death rate if results were limited to stage IV tumors and those having had previous treatment. A second paper reported that increased *MDR1* gene expression was associated with differentiation following retinoic acid treatment.

The session on differentiation included several papers on cell surface re-

ceptors. Many dealt with the presence of high affinity nerve growth factor receptor, or TRK, as it relates to prognosis and its response to retinoic acid treatment. Three papers showed that the presence of high TRK expression was associated with young age and low stage, and thus a significant survival advantage, and TRK may also play a role in mediating programmed cell death. Other papers showed that exposure to retinoic acid led to increased expression of TRK-A and TRK-B. Several papers dealt with the effects of retinoic acid on differentiation, and one compared the effects of 13-*cis*-retinoic acid to *trans*-retinoic acid on human neuroblastoma cell lines.

The third day of the symposium was devoted to more clinically related papers, including the results from megatherapy with bone marrow and peripheral stem cell rescue, and the role of 131-I-Meta-iodobenzylguanidine (MIBG). There were two papers on the use of monoclonal antibody treatment with or without radio labeling. Lastly, there were four papers and much discussion on the role of mass screening in the detection of neuroblastoma at a young age and possibly at a more treatable stage. The debate in this area revolved around the issue of whether patients with aggressive neuroblastoma actually start with the more benign form, and if so, could treatment prevent its progression to aggressive disease. The contrary stance, held by some, is that screening simply detects patients with favorable disease who require little or no treatment anyhow. It was obvious from the Japanese experience that an increased number of patients is picked up by screening, approximately twice that previously detected by clinical methods alone.

It is apparent that the enigmas of neuroblastoma have attracted an increasing number of laboratory scientists since the first conference 18 years ago. The basic mechanisms of favorable and unfavorable disease are being described. Their understanding will have wide repercussions. At the clinical level, more targeted forms of treatment will help achieve the basic aim of pediatric oncology — cure with minimum complications. At the fundamental level, time, unraveling the mysteries of this unique tumor, will provide greater insights into the nature of the malignant process itself.

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