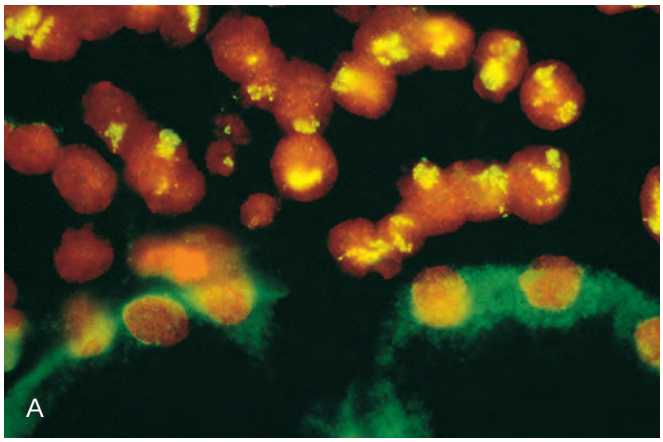
that cause deep blue discoloration of the skin (earning the unfortunate designation of "*blueberry muffin baby*"). *About 90% of neuroblastomas, regardless of location, produce catecholamines* (similar to the catecholamines associated with pheochromocytomas), which are an important diagnostic feature (i.e., elevated blood levels of catecholamines and elevated urine levels of the metabolites vanillylmandelic acid [VMA] and homovanillic acid [HVA]). Despite the elaboration of catecholamines, hypertension is much less frequent with these neoplasms than with pheochromocytomas (Chapter 24). Ganglioneuromas, unlike their malignant counterparts, tend to produce either asymptomatic mass lesions or symptoms related to compression.

The course of neuroblastomas is extremely variable. Several clinical, histopathologic, molecular, and biochemical factors have been identified that have a bearing on prognosis (Table 10-8); based on the collection of prognostic factors present in a given patient, they are classified either as "low," "intermediate," or "high" risk. With improvements in therapy, long-term survival exceeds 90% of patients in the first two groups, while less than 50% of patients in the high-risk category are long-term survivors. The most pertinent prognostic factors include the following:

- *Age and stage are the most important determinants of outcome.* Neuroblastomas at stages 1, 2A, or 2B tend to have an excellent prognosis, irrespective of age ("low" or "intermediate" risk); the one notable exception to this rule are tumors exhibiting amplification of the *MYCN* oncogene. Infants with localized primary tumors and widespread metastases to the liver, bone marrow, and skin (stage 4S) represent a special subtype, wherein it is not uncommon for the disease to regress spontaneously. The biologic basis of this welcome behavior is not clear. *The age of 18 months has emerged as a critical point of dichotomy in terms of prognosis.* Children younger than 18 months of age, and especially those in the first year of life, have an excellent prognosis regardless of the stage of the neoplasm. Children older than 18 months fall into at least the "intermediate" risk category, while those with higher stage tumors or with confounding unfavorable prognostic variables like *MYCN* amplification in the neoplastic cells are considered "high" risk.
- *Morphology is an independent prognostic variable in neuroblastic tumors.* An age-linked morphologic classification of neuroblastic tumors has recently been proposed that divides them into *favorable* and *unfavorable* histologic subtypes. The specific morphologic features that bear on prognosis are listed in Table 10-8.
- *Amplification of the MYCN oncogene in neuroblastomas is a molecular event that has possibly the most profound impact on prognosis,* particularly when it occurs in tumors that would otherwise portend a good outcome. The presence of *MYCN* amplification "bumps" the tumor into a "high"-risk category, irrespective of age, stage, or histology. *MYCN* is located on the distal short arm of chromosome 2 (2p23-p24). Amplification of *MYCN* does not karyotypically manifest at the resident 2p23-p24 site, but rather as extrachromosomal double minute chromosomes or homogeneously staining regions on other chromosomes (Fig. 10-27). *MYCN* amplification is present in about 20% to 30% of primary tumors, most presenting as advanced-stage disease, and the degree of amplification correlates with worse prognosis. *MYCN* amplification is currently the most important genetic abnormality used in risk stratification of neuroblastic tumors (see later).
- *Ploidy* of the tumor cells correlates with outcome in children less than 2 years of age but loses its independent prognostic significance in older children. Broadly, neuroblastomas can be divided into two categories: *near-diploid* and *hyper-diploid* (*whole chromosome gains*), with the latter being associated with a better prognosis. It is postulated that neuroblastomas with hyperdiploidy have an underlying defect in the mitotic machinery, leading to nondisjunction and whole chromosome gains, but otherwise relatively banal karyotypes. On the contrary, the more aggressive near-diploid tumors



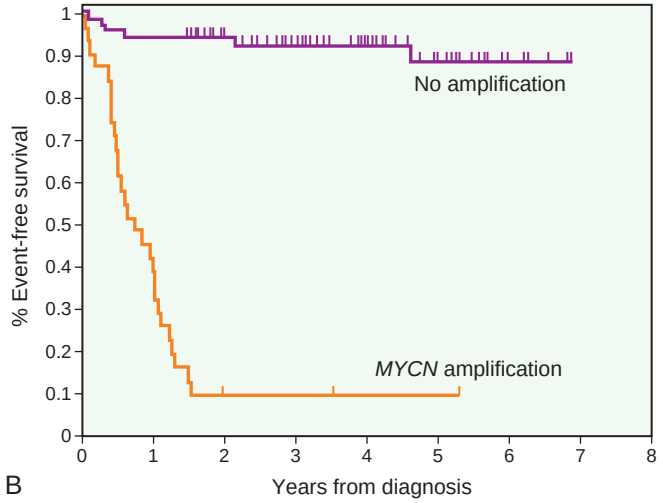


Figure 10-27 **A**, Fluorescence in situ hybridization using a fluorescein-labeled cosmid probe for *N-myc* on a tissue section. Note the neuroblastoma cells on the upper half of the photo with large areas of staining (*yellow-green*); this corresponds to amplified *N-MYC* in the form of homogeneously staining regions. Renal tubular epithelial cells in the lower half of the photograph show no nuclear staining and background (*green*) cytoplasmic staining. **B**, A Kaplan-Meier survival curve of infants younger than 1 year of age with metastatic neuroblastoma. The 3-year event-free survival of infants whose tumors lacked *MYCN* amplification was 93%, whereas those with tumors that had *MYCN* amplification had only a 10% event free survival. (**A,** Courtesy Dr. Timothy Triche, Children's Hospital, Los Angeles, Calif.; **B,** Reproduced with permission from Brodeur GM: Neuroblastoma: biological insights into a clinical enigma. Nat Rev Cancer 3:203-216; 2003.)