differentiation of primitive neuroblasts into mature elements, spontaneous tumor regression, and a *wide range of clinical behavior and prognosis*, which often mirror the extent of histologic differentiation. Neuroblastoma is the most important member of this family. It is the most common extracranial solid tumor of childhood, and the most frequently diagnosed tumor of infancy. The prevalence is about one case in 7000 live births, and there are approximately 700 cases diagnosed each year in the United States. The median age at diagnosis is 18 months; approximately 40% of cases are diagnosed in infancy. Most neuroblastomas occur sporadically, but 1% to 2% are familial, and in such cases the neoplasms may involve both of the adrenals or multiple primary autonomic sites. Germline mutations in the *anaplastic lymphoma kinase (ALK)* gene (Chapter 13) have recently been identified as a major cause of familial predisposition to neuroblastoma. Somatic gain-of-function *ALK* mutations are also observed in less than 10% of sporadic neuroblastomas. Tumors harboring *ALK* mutations in either the germline or somatic setting may be amenable to treatment using small molecule inhibitors that target the activity of this kinase.

Despite the remarkable progress made in the therapy of this disease, long-term prognosis for the high-risk subsets remains modest, with a 5-year survival in the range of 40%. As will be evident later, age and stage have a remarkable effect on prognosis, and, in general, children younger than 18 months of age tend to have a significantly better prognosis than older individuals at comparable disease burdens.

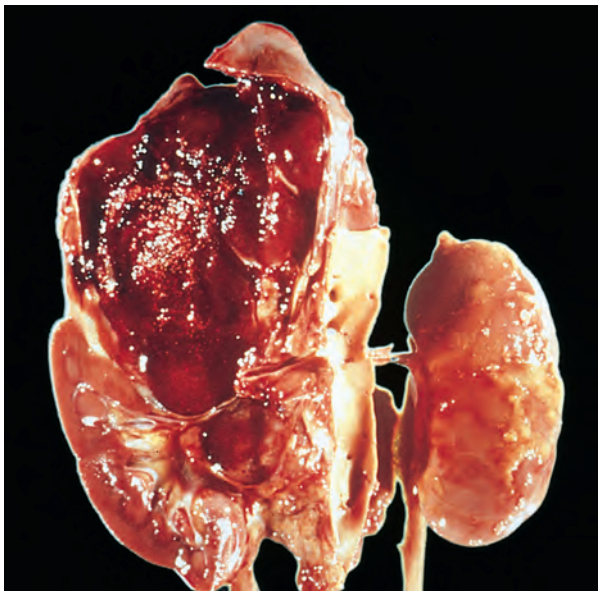

Figure 10-24 Adrenal neuroblastoma in a 6-month-old child. The hemorrhagic, partially encapsulated tumor has displaced the opened left kidney and is impinging on the aorta and left renal artery. (Courtesy Dr. Arthur Weinberg, University of Texas Southwestern Medical School, Dallas, Texas.)

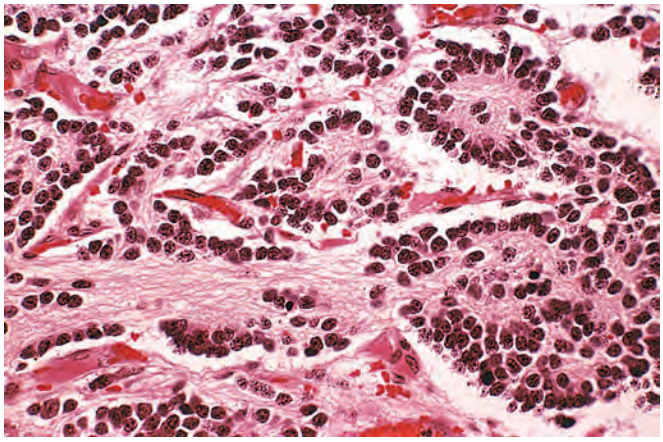

Figure 10-25 Adrenal neuroblastoma. This tumor is composed of small cells embedded in a finely fibrillar matrix.

MORPHOLOGY

In childhood about 40% of neuroblastomas arise in the adrenal medulla. The remainder occur anywhere along the sympathetic chain, with the most common locations being the paravertebral region of the abdomen (25%) and posterior mediastinum (15%). Tumors may arise in numerous other sites, including the pelvis, the neck, and within the brain (cerebral neuroblastomas).

Neuroblastomas range in size from minute nodules (so-called **in situ lesions**) to large masses more than 1 kg in weight (Fig. 10-24). In situ neuroblastomas are reported to occur 40 times more frequently than clinically overt tumors. The great majority of these silent lesions spontaneously regress, leaving only a focus of fibrosis or calcification in the adult; this has led some to question the neoplastic connotation for the in situ lesions, arguing instead in favor of labeling them as developmental anomalies ("rests").

Some neuroblastomas are often sharply demarcated by a fibrous pseudo-capsule, but others are far more infiltrative and invade surrounding structures, including the kidneys, renal vein, and vena cava, and envelop the aorta. On transection, they are composed of soft, gray-tan, tissue. Larger tumors have areas of necrosis, cystic softening, and hemorrhage. Occasionally, foci of punctate intra-tumoral calcification can be palpated.

Histologically, classic neuroblastomas are composed of small, primitive-appearing cells with dark nuclei, scant cytoplasm, and poorly defined cell borders growing in solid sheets. Such tumors may be difficult to differentiate morphologically from other small round blue cell tumors. Mitotic activity, nuclear breakdown ("karyorrhexis"), and pleomorphism may be prominent. The background often demonstrates a faintly eosinophilic fibrillary material (**neuropil**) that corresponds to neuritic processes of the primitive neuroblasts. Typically, rosettes (**Homer-Wright pseudorosettes**) can be found in which the tumor cells are concentrically arranged about a central space filled with neuropil (Fig. 10-25). Other helpful features include positive immunohistochemical reactions for neuron-specific enolase and ultrastructural demonstration of small, membrane-bound, cytoplasmic catecholamine-containing secretory granules; the latter contain characteristic central dense cores surrounded by a peripheral halo (dense core granules). Some neoplasms show signs of maturation that can be spontaneous or therapy-induced. Larger cells having more abundant cytoplasm, large vesicular nuclei, and a prominent nucleolus, representing *ganglion cells* in various stages of maturation, may be found in tumors admixed with primitive neuroblasts (**ganglioneuroblastoma**). Even better differentiated lesions contain many more