syndrome represents the "first hit"; the development of Wilms tumor in these patients frequently correlates with the occurrence of a nonsense or frameshift mutation in the second *WT1* allele ("second hit").

- A second group of patients at much higher risk for Wilms tumor (~90%) have the *Denys-Drash syndrome*, which is characterized by *gonadal dysgenesis* (male pseudohermaphroditism) and *early-onset nephropathy* leading to renal failure. The characteristic glomerular lesion in these patients is a *diffuse mesangial sclerosis* (Chapter 20). As in patients with WAGR, these patients also demonstrate germline abnormalities in *WT1.* In patients with the Denys-Drash syndrome, however, the genetic abnormality is a *dominant-negative missense mutation* in the zinc-finger region of the WT1 protein that affects its DNA-binding properties. This mutation interferes with the function of the remaining wild-type allele, yet strangely, it is sufficient only in causing genitourinary abnormalities, but not tumorigenesis; Wilms tumors arising in Denys-Drash syndrome demonstrate bi-allelic inactivation of *WT1.* In addition to Wilms tumors, these individuals are also at increased risk for developing germ cell tumors called *gonadoblastomas* (Chapter 21), almost certainly a consequence of disruption in normal gonadal development.

  WT1 encodes a DNA-binding transcription factor that is expressed within several tissues, including the kidney and gonads, during embryogenesis. The WT1 protein is critical for normal renal and gonadal development. WT1 has multiple binding partners, and the choice of this partner can affect whether WT1 functions as a transcriptional activator or repressor in a given cellular context. Numerous transcriptional targets of WT1 have been identified, including genes encoding glomerular podocyte-specific proteins and proteins involved in induction of renal differentiation. Despite the importance of *WT1* in nephrogenesis and its unequivocal role as a tumor suppressor gene, only about 10% of patients with sporadic (nonsyndromic) Wilms tumors demonstrate *WT1* mutations, suggesting that the majority of these tumors are caused by mutations in other genes.
- A third group, that is clinically distinct from these previous two groups of patients but also with an increased risk of developing Wilms tumor are children with *Beckwith-Wiedemann syndrome* (BWS), characterized by enlargement of body organs (organomegaly), macroglossia, hemihypertrophy, omphalocele, and abnormal large cells in the adrenal cortex (adrenal cytomegaly). BWS has served as a model for a nonclassical mechanism of tumorigenesis in humans—*genomic imprinting* (Chapter 5). The chromosomal region implicated in BWS has been localized to band 11p15.5 ("WT2"), distal to the *WT1* locus. This region contains multiple genes that are normally expressed from only one of the two parental alleles, with transcriptional silencing (i.e., imprinting) of the other parental homologue by methylation of the promoter region. Unlike WAGR or Denys-Drash syndromes, the genetic basis for BWS is considerably more heterogeneous in that no single 11p15.5 gene is involved in all cases. Moreover, the phenotype of BWS, including the predisposition to tumorigenesis, is influenced by the specific "WT2" imprinting abnormalities present. One of the genes in this region—insulin-like growth factor-2 (*IGF2*)—is normally expressed solely from the *paternal allele*, while the maternal allele is silenced by imprinting. In some Wilms tumors, *loss of imprinting* (i.e., re-expression of the maternal *IGF2* allele) can be demonstrated, leading to overexpression of the IGF-2 protein. In other instances there is a selective deletion of the imprinted maternal allele, combined with duplication of the transcriptionally active paternal allele in the tumor *(uniparental paternal disomy)*, which has an identical functional effect in terms of overexpression of IGF-2. Because the IGF-2 protein is an embryonal growth factor, it could conceivably explain the features of overgrowth associated with BWS, as well as the increased risk for Wilms tumors in these patients. Of all the "WT2" genes, imprinting abnormalities of *IGF2* have the strongest relationship to tumor predisposition in BWS. A subset of patients with BWS harbor mutations of the cell cycle regulator *CDKN1C* (also known as *p57* or *KIP2*); however, these patients have a significantly lower risk for developing Wilms tumors. In addition to Wilms tumors, patients with BWS are also at increased risk for developing hepatoblastoma, pancreatoblastoma, adrenocortical tumors, and rhabdomyosarcomas.

Recent genetic studies have also elucidated the role of β-catenin in Wilms tumor. It will be recalled (Chapter 7) that β-catenin belongs to the developmentally important *WNT (wingless)* signaling pathway. Gain-of-function mutations of the gene encoding β-catenin have been demonstrated in approximately 10% of sporadic Wilms tumors; there is a significant overlap between the presence of *WT1* and β-catenin mutations, suggesting a synergistic role for these events in the genesis of Wilms tumors.

Nephrogenic rests are putative precursor lesions of Wilms tumors and are seen in the renal parenchyma adjacent to approximately 25% to 40% of unilateral tumors; this frequency rises to nearly 100% in cases of bilateral Wilms tumors. In many instances the nephrogenic rests share genetic alterations with the adjacent Wilms tumor, pointing to their preneoplastic status. The appearance of nephrogenic rests varies from expansile masses that resemble Wilms tumors (hyperplastic rests) to sclerotic rests consisting predominantly of fibrous tissue and occasional admixed immature tubules or glomeruli. It is important to document the presence of nephrogenic rests in the resected specimen, because these patients are at an increased risk of developing Wilms tumors in the contralateral kidney and require frequent and regular surveillance for many years.

MORPHOLOGY

Grossly, Wilms tumor tends to present as a large, solitary, well-circumscribed mass, although 10% are either bilateral or multicentric at the time of diagnosis. On cut section, the tumor is soft, homogeneous, and tan to gray with occasional foci of hemorrhage, cyst formation, and necrosis (Fig. 10-28).

Microscopically, Wilms tumors are characterized by recognizable attempts to recapitulate different stages of nephrogenesis. **The classic triphasic combination of blastemal, stromal, and epithelial cell types is observed in the vast majority**