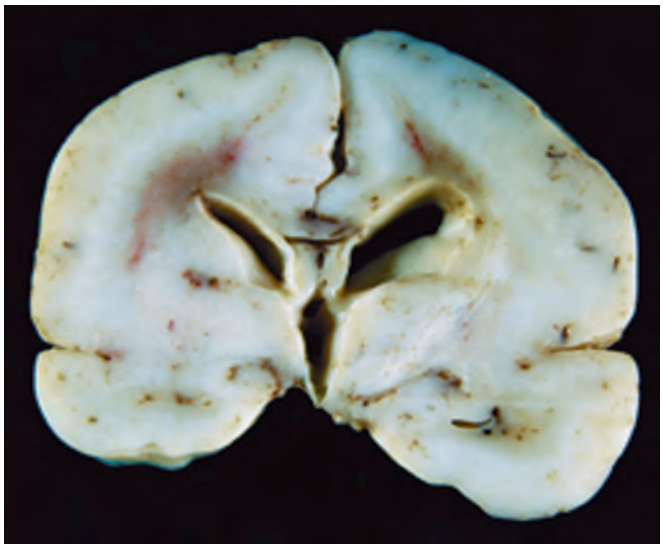

**Figure 28-5** Lissencephaly. The absence of cortical gyri defines this abnormality, seen here in the brain from a full-term infant.

- The volume of brain may be abnormally large *(megalencephaly)* or abnormally small *(microencephaly)*. Microencephaly, by far the more common of the two, is typically accompanied by a small head circumference. It can be associated with a number of conditions, including chromosome abnormalities, fetal alcohol syndrome, and human immunodeficiency virus 1 (HIV-1) infection acquired in utero. It is postulated that the underlying anomaly is a reduction in the number of neurons that reach the neocortex and this leads to a simplification of the gyral folding, a model supported by experimental results in mouse models.
- *Lissencephaly* is a malformation characterized by reduction in the number of gyri, which in the extreme case may show no gyral pattern *(agyria)* (Fig. 28-5). Two general patterns are observed, a smooth surfaced form (type 1), and a rough or cobblestoned surfaced form (type 2). In general, type 1 forms are associated with mutations that disrupt the signaling for migration and the cytoskeletal "motor" proteins that drive migration of neuroblasts. In contrast, type 2 lissencephaly is most commonly associated with genetic alterations that disrupt the "stop signal" for migration. This signal depends on a set of specifically glycosylated proteins, and mutations in the enzymes that place the sugars onto the proteins are the most common causes of this form of lissencephaly.
- *Polymicrogyria* is characterized by small, unusually numerous, irregularly formed cerebral convolutions. The gray matter is composed of four layers (or fewer), with entrapment of apparent meningeal tissue at points of fusion that would otherwise be the cortical surface. Polymicrogyria can be induced by localized tissue injury toward the end of neuronal migration, although genetically determined forms, which are typically bilateral and symmetric, are also recognized.
- *Neuronal heterotopias* are a group of migrational disorders that are commonly associated with epilepsy. They are defined by the presence of collections of neurons in inappropriate locations along the pathway of migration. As might be expected, one location in which heterotopias can be found is along the ventricular surface—as though the cells never managed to leave their place of birth. Periventricular heterotopias can be caused by mutations in the gene encoding filamin A, an actin-binding protein responsible for assembly of complex meshworks of filaments. This gene is on the X chromosome, and the mutant allele causes male lethality; in females the process of X inactivation separates neurons into those with a normal allele (in the correct location) and those with the mutant allele (in the heterotopia). Another microtubule-associated protein, doublecortin (DCX), is also encoded by a gene on the X chromosome; mutations in this gene result in lissencephaly in males and in subcortical band heterotopias in females. These heterotopias may consist of discrete nodules of neurons sitting in the subcortical white matter or complete ribbons that parody the overlying cortex.
- *Holoprosencephaly* is a spectrum of malformations characterized by incomplete separation of the cerebral hemispheres across the midline. Severe forms manifest midline facial abnormalities, including cyclopia; less severe variants (*arrhinencephaly*) show absence of the olfactory cranial nerves and related structures. Intrauterine diagnosis of severe forms by ultrasound examination is now possible. Holoprosencephaly is associated with trisomy 13 as well as other genetic syndromes. Mutations in genes that encode components of the sonic hedgehog signaling pathway may result in holoprosencephaly.
- *Agenesis of the corpus callosum*, a relatively common malformation, refers to the absence of the white matter bundles that carry cortical projections from one hemisphere to the other (Fig. 28-6). Radiologic imaging studies show misshapen lateral ventricles ("bat-wing" deformity); on coronal whole-mount sections of the brain, bundles of anteroposteriorly oriented white

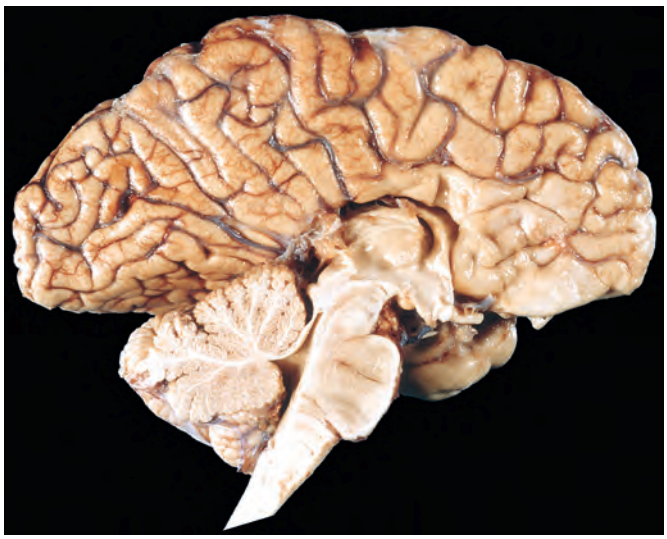

**Figure 28-6** Agenesis of the corpus callosum. The midsagittal view of the left hemisphere shows the lack of a corpus callosum and cingulate gyrus above the third ventricle.