occasionally, life-threatening complications. These patients have other features of classic cystic fibrosis, such as pulmonary disease. By contrast, *"idiopathic" chronic pancreatitis* can also occur as an isolated late-onset finding in the absence of other stigmata of cystic fibrosis (Chapter 19); bi-allelic *CFTR* mutations (usually one "mild," one "severe") are demonstrable in the majority of these individuals who have *nonclassic or atypical cystic fibrosis. Endocrine pancreatic insufficiency* (i.e., diabetes) is uncommon in cystic fibrosis and is caused by severe destruction of pancreatic parenchyma including the islets.

Cardiorespiratory complications, such as persistent lung infections, obstructive pulmonary disease, and *cor pulmonale*, are the most common cause of death (~80%) in patients in the United States. By age 18, 80% of patients with classic cystic fibrosis harbor *P. aeruginosa*, and 3.5% harbor *B. cepacia*. With the indiscriminate use of antibiotic prophylaxis against *Staphylococcus*, there has been an unfortunate resurgence of resistant strains of *Pseudomonas* in many patients. Individuals who carry one "severe" and one "mild" *CFTR* mutation may develop late-onset mild pulmonary disease, another example of nonclassic or atypical cystic fibrosis. Patients with mild pulmonary disease usually have little or no pancreatic disease. Adult-onset "*idiopathic*" *bronchiectasis*, has been linked to *CFTR* mutations in a subset of cases. *Recurrent sinonasal polyps* can occur in 10% to 25% of individuals with cystic fibrosis; hence, children who present with this finding should be tested for cystic fibrosis.

Significant *liver disease* occurs late in the natural history of cystic fibrosis and is gaining in clinical importance as life expectancies increase. In fact, after cardiopulmonary and transplantation-related complications, liver disease is the most common cause of death in cystic fibrosis. Most studies suggest that symptomatic or biochemical liver disease has its onset at or around puberty, with a prevalence of approximately 13% to 17%. However, *asymptomatic hepatomegaly* may be present in up to a third of individuals. Obstruction of the common bile duct may occur due to stones or sludge; it presents with abdominal pain and the acute onset of jaundice. As previously noted, *diffuse biliary cirrhosis* develops in less than 10% of individuals with cystic fibrosis.

Approximately 95% of males with cystic fibrosis are *infertile*, as a result of obstructive azoospermia. As mentioned earlier, this is most commonly due to congenital bilateral absence of the vas deferens, which is caused in 80% of cases by bi-allelic *CFTR* mutations.

In most cases, the diagnosis of cystic fibrosis is based on persistently elevated sweat electrolyte concentrations (often the mother makes the diagnosis by recognizing her infant's abnormally salty sweat), characteristic clinical findings (sinopulmonary disease and gastrointestinal manifestations), an abnormal newborn screening test, or a family history. A minority of patients with cystic fibrosis, especially those with at least one "mild" *CFTR* mutation, may have a normal or near-normal sweat test (<60 mM/L). Measurement of nasal transepithelial potential difference in vivo can be a useful adjunct under these circumstances; individuals with cystic fibrosis demonstrate a significantly more negative baseline nasal potential difference than controls. Sequencing the *CFTR* gene is the gold standard for diagnosis of cystic fibrosis. Therefore, in patients with suggestive clinical findings or family history (or both), genetic analysis may be warranted.

There have been major improvements in the management of acute and chronic complications for cystic fibrosis, including more potent antimicrobial therapies, pancreatic enzyme replacement, and bilateral lung transplantation. New treatment modalities for restoring mutant CFTR function are being tested in clinical trials. For example, the first-in-class of a group of agents known as CFTR "potentiators" has been recently approved for use in a minority (~3%-5%) of cystic fibrosis patients that harbor a G155D mutation in the *CFTR* gene. This particular mutation is a class IV alteration, in which functionally defective CFTR is present in otherwise normal amounts at the cell membrane; the orally bioavailable CFTR "potentiator" partially restores the critical ion transport functions to the defective channel. Overall, improvements in the management of cystic fibrosis has extended the median life expectancy to close to 40 years and increasingly, a lethal disease of childhood is changing into a chronic disease of adults.

Sudden Infant Death Syndrome (SIDS)

According to the National Institute of Child Health and Human Development, **SIDS is defined as "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history."** It is important to emphasize that many cases of sudden death in infancy may have an unexpected anatomic or biochemical basis discernible at autopsy (Table 10-6), and these should not be labeled as SIDS, but rather as *sudden unexpected infant death (SUID).* The Centers for Disease Control and Prevention estimates that SIDS accounts for approximately half of the cases of SUID in the United States. An aspect of SIDS that is not stressed in the definition is that the infant usually dies while asleep, mostly in the prone or side position, hence the pseudonyms of *crib death* or *cot death.*

Epidemiology. As infantile deaths due to nutritional problems and infections have come under control in developed countries, SIDS has assumed greater importance, including in the United States. SIDS is the leading cause of death between age 1 month and 1 year in this country and the third leading cause of death overall in infancy, after congenital anomalies and diseases of prematurity and low birth weight. Mostly because of nationwide SIDS awareness campaigns by organizations such as the American Academy of Pediatrics, there has been a significant drop in SIDS-related mortality in the past decade, from an estimated 120 deaths per 100,000 live births in 1992 to 54 per 100,000 in 2005. This number translates to about 2000 deaths due to SIDS in the US. Worldwide, in countries where unexpected infant deaths are diagnosed as SIDS only after postmortem examination, the death rates from SIDS range from 10 per 100,000 live births in the Netherlands to 80 per 100,000 in New Zealand.

Approximately 90% of all SIDS deaths occur during the first 6 months of life, most between ages 2 and 4 months. This narrow window of peak susceptibility is a unique characteristic that is independent of other risk factors (to