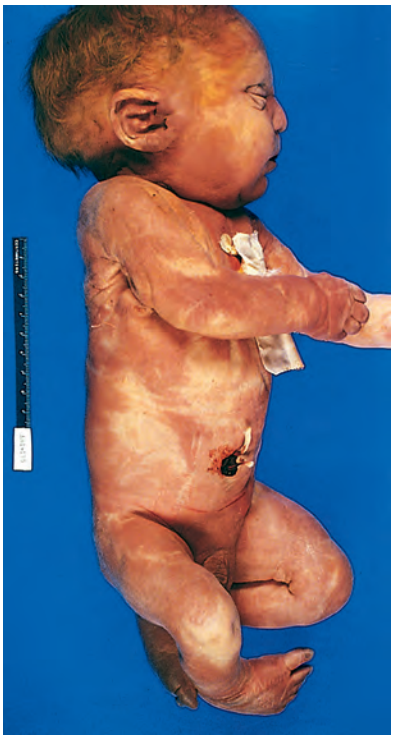

Figure 10-4 Infant with oligohydramnios sequence. Note the flattened facial features and deformed right foot (talipes equinovarus).

refers to the complete absence of an organ and its associated primordium. A closely related term, aplasia, also refers to the absence of an organ but one that occurs due to failure of growth of the existing primordium. *Atresia* describes the absence of an opening, usually of a hollow visceral organ, such as the trachea and intestine. *Hypoplasia* refers to incomplete development or decreased size of an organ with decreased numbers of cells, whereas *hyperplasia* refers to the converse, that is, the enlargement of an organ due to increased numbers of cells. An abnormality in an organ or a tissue as a result of an increase or a decrease in the size (rather than the number) of individual cells defines *hypertrophy* or *hypotrophy*, respectively. Finally, *dysplasia*, in the context of malformations (versus *neoplasia*) describes an abnormal organization of cells.

Causes of Anomalies

At one time, it was believed that the presence of a visible, external anomaly was divine punishment for wickedness, a belief that occasionally jeopardized the mother's life. Although we are learning a great deal about the molecular bases of some congenital anomalies, *the exact cause remains unknown in at least one half to three fourths of the cases.* **The common known causes of congenital anomalies can be grouped into three major categories: genetic, environmental, and multifactorial** (Table 10-2).

Genetic causes of malformations include all of the previously discussed mechanisms of genetic disease (Chapter 5). Virtually all chromosomal syndromes are associated with congenital malformations. Examples include Down syndrome and other trisomies, Turner syndrome, and Klinefelter syndrome. Most chromosomal disorders arise during gametogenesis and hence are not familial. Single-gene mutations, characterized by mendelian inheritance, may underlie major malformations. For example, holoprosencephaly is the most common developmental defect of the forebrain and midface in humans; the Hedgehog signaling pathway plays a critical role in the morphogenesis of these structures, and loss-of-function mutations of individual components within this pathway are reported in families with a history of recurrent holoprosencephaly.

Table 10-2 Causes of Congenital Anomalies in Humans

Cause	Frequency (%)
Genetic	
Chromosomal aberrations	10-15
Mendelian inheritance	2-10
Environmental	
Maternal/placental infections Rubella Toxoplasmosis Syphilis Cytomegalovirus Human immunodeficiency virus	2-3
Maternal disease states Diabetes Phenylketonuria Endocrinopathies	6-8
Drugs and chemicals Alcohol Folic acid antagonists Androgens Phenytoin Thalidomide Warfarin 13-*cis*-retinoic acid Others	1
Irradiations	1
Multifactorial	20-25
Unknown	40-60

Adapted from Stevenson RE, et al (eds): Human Malformations and related Anomalies. New York, Oxford University Press, 1993, p 115.

Environmental influences, such as viral infections, drugs, and irradiation to which the mother was exposed during pregnancy, may cause fetal anomalies. Among the viral infections listed in Table 10-2, rubella was a major scourge of the nineteenth and early twentieth centuries. Fortunately, maternal rubella and the resultant *rubella embryopathy* have been virtually eliminated in developed countries as a result of maternal rubella vaccination. A variety of drugs and chemicals have been suspected to be teratogenic, but perhaps less than 1% of congenital malformations are caused by these agents. The list includes thalidomide, alcohol, anticonvulsants, warfarin (oral anticoagulant), and 13-*cis*-retinoic acid, which is used in the treatment of severe acne. For example, *thalidomide,* once used as a tranquilizer in Europe, causes an extremely high incidence (50% to 80%) of limb malformations. *Alcohol,* when consumed even in modest amounts during pregnancy, is an important environmental teratogen. Affected infants show prenatal and postnatal growth retardation, facial anomalies (microcephaly, short palpebral fissures, maxillary