The medical science of genetics continues to advance at a rapid pace with new techniques and discoveries being made constantly. The U.S. genome project, \(^1\) begun in 1990 as a joint effort between the National Institutes of Health and the U.S. Department of Energy, has further accelerated the progress of identifying more metabolic and genetic diseases at an even earlier stage of development. After the working draft of the entire human genome sequence was published recently, \(^2\) researchers have become very excited about the potential to uncover the genetic basis of many diseases—this is particularly interesting in the context of prenatal diagnosis of diseases. A number of methods are currently being utilized to evaluate the fetus, and the future will yield more reasons to exploit this technology. In caring for these patients, we need to understand this technology not only to better care for our patients now but because we will soon be treating more and more fetuses as a result of the prenatal diagnosis.

Approximately 3% to 5% of all neonates have a known birth defect, \(^3\) and although most of these do not have known causes (Table 2.1), many can be detected before birth. The incidence of chromosomal abnormalities in live-born infants is estimated to be approximately 1 of 170 births. \(^4\) Since the discovery in the 1950s that Down syndrome is caused by an extra chromosome 21, the field of cytogenetics has grown enormously. Chromosomal abnormalities have been divided into three groups: numerical, structural, and mosaic.

**Types of Abnormalities**

**Numerical Chromosomal Abnormalities**

In this group, the number of chromosomes is either more or less than 46. Down syndrome is the most common numerical chromosomal abnormality. Klinefelter syndrome (47, XXY) and Turner syndrome (46, X) are other examples. Trisomy 13 and trisomy 18 also have recognizable patterns of malformations; other autosomal trisomies are rarely seen in live births.

**Structural Chromosomal Abnormalities**

Here, a specific region on a particular chromosome is altered in some way. Structural chromosomal abnormalities can occur in a variety of ways when chromosomal material is deleted, duplicated, or rearranged. For example, cri du chat syndrome is caused by the deletion of genetic material on chromosome 5. Translocations, rearrangements of material between chromosomes, are probably the most clinically significant type of chromosomal rearrangement that cause structural chromosomal changes.

**Mosaic Chromosomal Abnormalities**

Chromosome mosaicism is the presence of two (or more) cytogenetically distinct cell lines in the same individual caused by an error during early mitosis of the zygote after conception. A number of techniques, including ultrasound, amniocentesis, chorionic villus sampling, fetal blood sampling, maternal blood sampling, and magnetic resonance imaging (MRI), are currently in use to make accurate prenatal diagnosis of fetal disorders.

**Ultrasound**

High-resolution ultrasonography has had a profound impact on the practice of obstetrics in a variety of applications, including the detection of fetal anomalies. Although most experts have traditionally recommended employing ultrasound after 18 weeks of gestation because of better visualization of the major organs, other authors have been utilizing ultrasound at even earlier ages. \(^5\) Many authorities have reported successful imaging of the major organ systems at 14 weeks or earlier. \(^5\) \(^6\) Continued advances in technology and in our understanding of fetal anomalies, will allow earlier and earlier detection of fetal defects.

Ultrasound works by generating intermittent high-frequency sound waves by applying an alternating electrical current to a transducer made of piezoelectric material. \(^7\) The transducer...
sends a pulse of sound waves that passes through the skin and soft tissues until it encounters an interface of different tissue densities. When this happens, a portion of the sound energy, proportional to the difference in densities at the interface, is reflected back to the transducer. This reflection of sound at the transducer creates an electrical voltage that is amplified onto a screen. In current ultrasonography, multiple transducers generate many sound waves simultaneously or in sequence to create real-time images to detect movement. This method allows monitoring not only of static fetal defects but also of fetal movements, breathing, or cardiac motions, and even blood vessel pulsation deficits.

The number of fetal anomalies detectable by high-resolution ultrasonography continues to grow (Table 2.2). Ultrasound has become popular because of its utility as well as because this information can be gathered with no known side effects to the mother or the fetus.

### Amniocentesis

Amniocentesis is the invasive prenatal diagnostic test most commonly used for genetic disease. The technique is considered to be relatively simple and is performed transabdominally with the use of ultrasonography. A 20- or 22-gauge needle is inserted into the amniotic cavity, withdrawing 20 to 30 mL of fluid to garner cells to culture. The fluid can also be used, for example, to assess fetal lung maturity. Amniocentesis for culturing cells is most commonly performed at midtrimester (16–18 weeks gestation). The most commonly cited risks are as follows:

- Preterm premature rupture of membranes (and possible resultant fetal loss)
- Infection
- Fetal trauma

Another risk involves bleeding into the placenta and into the amniotic sac. Any perforation of the placenta can lead to transfer of fetal blood to the mother and cause maternal immunization. Ultrasonic localization of the placenta can reduce the incidence of placental perforation, but anti-D globulin must be administered prophylactically to Rh-negative women at the time of amniocentesis.

### Chorionic Villus Sampling

Chorionic villus biopsies involve a similar approach to that of amniocentesis, except that a sample of the chorionic villus is aspirated by placing a transabdominal needle or a transvaginal catheter into the center of the chorion. The chorion is of fetal origin, and biopsies thus can be evaluated as can those obtained via amniocentesis. The advantage of chorionic villus biopsy is that fetal cells are obtained quickly and the normally long culture procedure is not needed because these chorion cells divide rapidly. Chorionic villus sampling has become the standard for either a first trimester alternative to amniocentesis or when amniocentesis has failed to yield adequate cells. There has been some controversy as to whether chorionic villus sampling is as safe as amniocentesis and whether the transcervical or transabdominal approach is better. It appears that chorionic villus sampling places the mother at slightly higher risk of fetal loss than amniocentesis.

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**Table 2.1.** Suspected etiologies of fetal congenital birth defects.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage (%) of all birth defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>20–25</td>
</tr>
<tr>
<td>Fetal infections</td>
<td>3–5</td>
</tr>
<tr>
<td>Maternal diseases</td>
<td>3–5</td>
</tr>
<tr>
<td>Medications/drugs</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>70–75</td>
</tr>
</tbody>
</table>


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**Table 2.2.** Fetal anomalies detectable by high-resolution ultrasonography.

- Cardiac (using echocardiography)
  - Atrial septal defect/ventricle septal defect
  - Valvular lesions
  - Pulmonary artery stenosis
  - Transposition of the great vessels
  - Hypoplastic left heart
  - Pericardial and pleural effusion
  - Fetal arrhythmias
  - Combined lesions (e.g., tetralogy of Fallot)

- Central nervous system
  - Hydrocephalus
  - Anencephaly
  - Encephalocele
  - Intracranial lesions
  - Meningocele
  - Meningomyelocele
  - Choroid plexus cysts

- Gastrointestinal
  - Diaphragmatic hernia
  - Omphalocele
  - Gastroesphageal fistula
  - Esophageal atresia
  - Duodenal atresia

- Urinary tract
  - Hydronephrosis/hydroureter
  - Renal agenesis/hypoplasia
  - Urethral valves
  - Polycystic/multicystic kidneys

- Skeletal
  - Achondroplasia
  - Osteogenesis imperfecta
  - Agenesis/hypoplasia of bones

- Other
  - Teratomas
  - Cleft lip
  - Fetal growth retardation

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Another problem associated with chorionic villus sampling is...