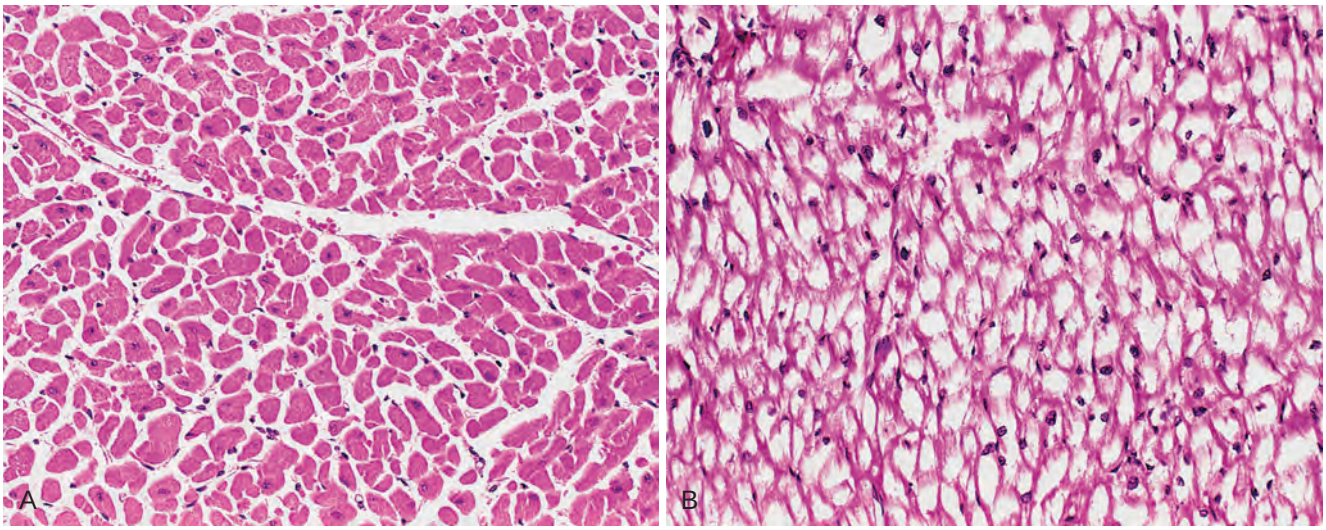

Figure 5-16 Pompe disease (glycogen storage disease type II). **A,** Normal myocardium with abundant eosinophilic cytoplasm. **B,** Patient with Pompe disease (same magnification) showing the myocardial fibers full of glycogen seen as clear spaces. (Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)

Complex Multigenic Disorders

As discussed previously, such disorders are caused by interactions between variant forms of genes and environmental factors. A gene that has at least two alleles, each of which occurs at a frequency of at least 1% in the population, is polymorphic, and each variant allele is referred to as a polymorphism. According to the common disease/common variant hypothesis, complex genetic disorders occur when many polymorphisms, each with a modest effect and low penetrance, are co-inherited. Two additional facts that have emerged from studies of common complex disorders, such as type 1 diabetes, are:

- While complex disorders result from the collective inheritance of many polymorphisms, different polymorphisms vary in significance. For example, of the 20 to 30 genes implicated in type 1 diabetes, six to seven are most important, and a few HLA-alleles contribute more than 50% of the risk (Chapter 24).
- Some polymorphisms are common to multiple diseases of the same type, while others are disease specific. This is best illustrated in immune-mediated inflammatory diseases (Chapter 6).

Several normal phenotypic characteristics are governed by multifactorial inheritance, such as hair color, eye color, skin color, height, and intelligence. These characteristics show a continuous variation in population groups, producing the standard bell-shaped curve of distribution. Environmental influences, however, significantly modify the phenotypic expression of complex traits. For example, type 2 diabetes mellitus has many of the features of a multifactorial disorder. It is well recognized that individuals often first manifest this disease after weight gain. Thus, obesity as well as other environmental influences unmasks the diabetic genetic trait. Nutritional influences may cause even monozygous twins to achieve different heights. The culturally deprived child cannot achieve his or her full intellectual capacity.

Assigning a disease to this mode of inheritance must be done with caution. It depends on many factors but first on familial clustering and the exclusion of Mendelian and chromosomal modes of transmission. A range of levels of severity of a disease is suggestive of a complex multigenic disorder, but, as pointed out earlier, variable expressivity and reduced penetrance of single mutant genes may also account for this phenomenon. Because of these problems, sometimes it is difficult to distinguish between Mendelian and multifactorial disease.

Chromosomal Disorders

Normal Karyotype

As you will remember, human somatic cells contain 46 chromosomes; these comprise 22 homologous pairs of autosomes and two sex chromosomes, XX in the female and XY in the male. The study of chromosomes—*karyotyping*—is the basic tool of the cytogeneticist. The usual procedure to examine chromosomes is to arrest dividing cells in metaphase with mitotic spindle inhibitors (e.g., *N*-diacetyl-*N*-methylcolchicine [Colcemid]) and then to stain the chromosomes. In a metaphase spread, the individual chromosomes take the form of two chromatids connected at the centromere. A karyotype is obtained by arranging each pair of autosomes according to length, followed by sex chromosomes.

A variety of staining methods have been developed that allow identification of individual chromosomes on the basis of a distinctive and reliable pattern of alternating light and dark bands. The one most commonly used involves a Giemsa stain and is hence called *G banding*. A normal male karyotype with G banding is illustrated in Figure 5-17. With standard G banding, approximately 400 to 800 bands per haploid set can be detected. The resolution obtained by banding can be markedly improved by obtaining the cells in prophase. The individual chromosomes appear markedly elongated, and as many as 1500 bands