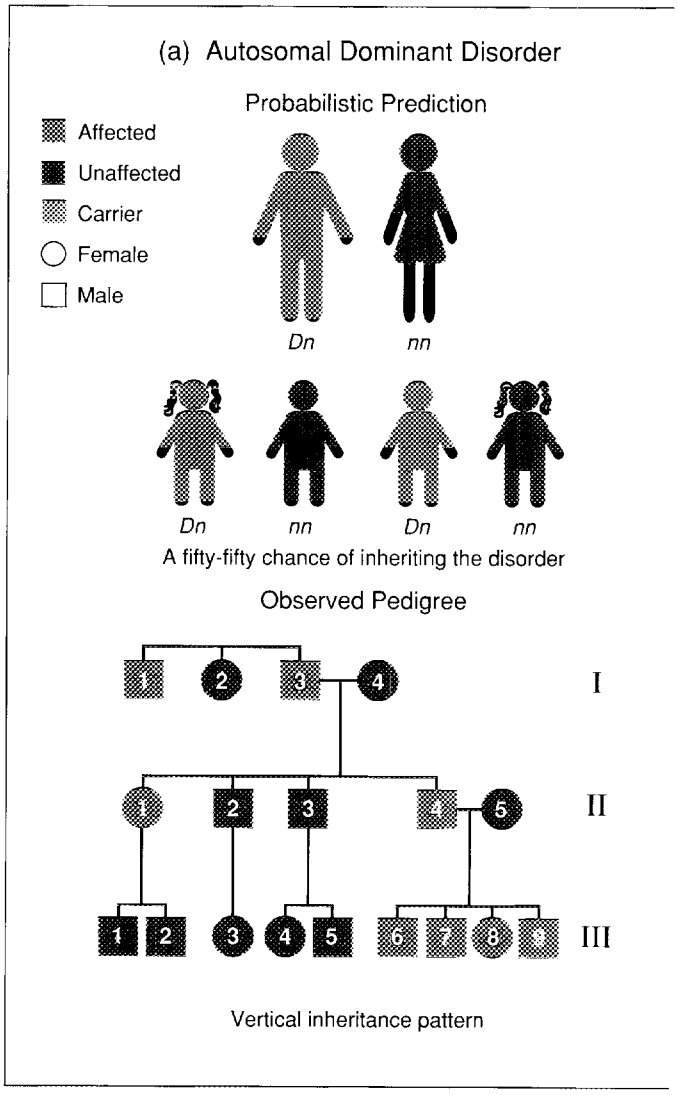
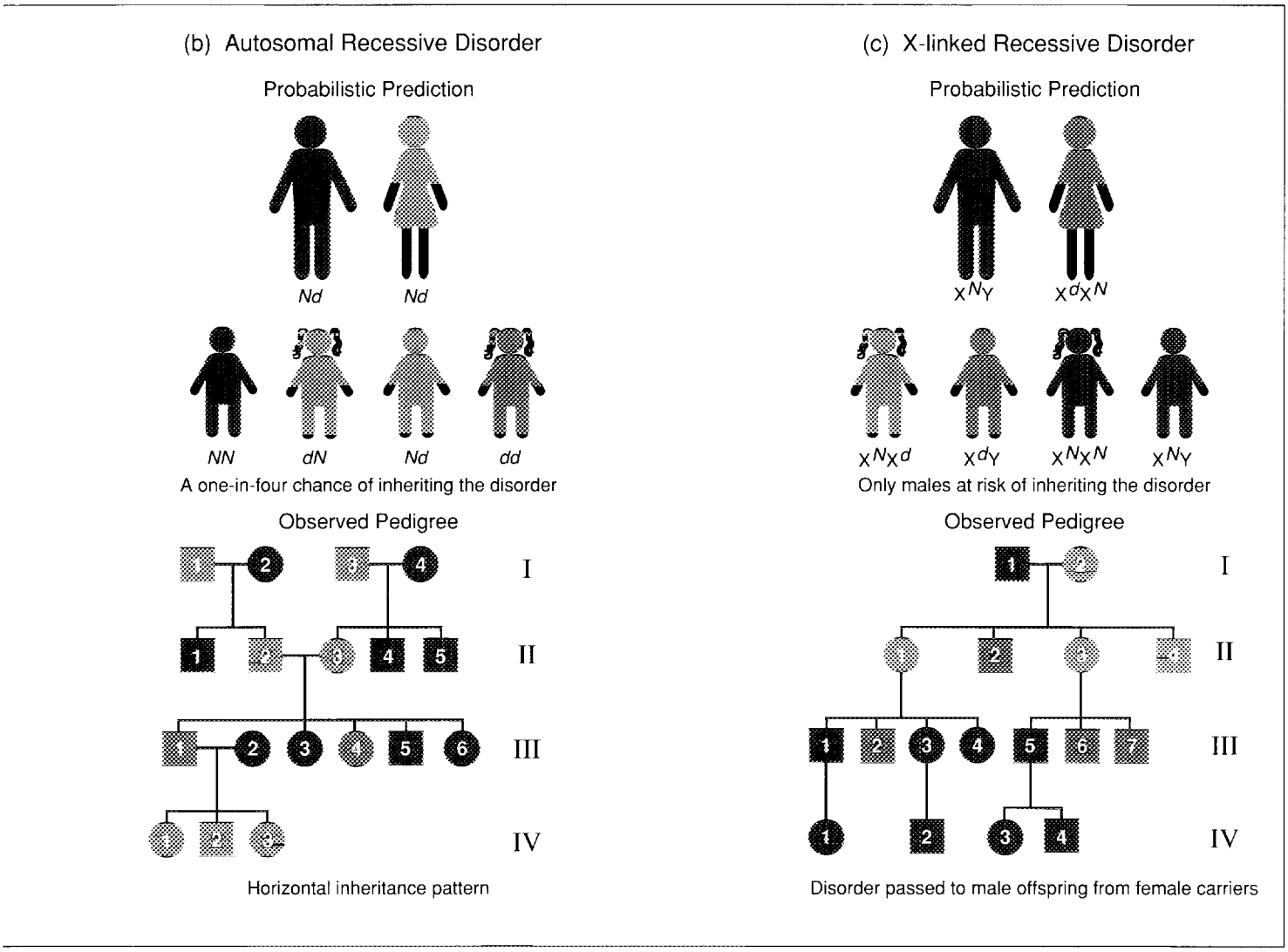
INHERITANCE OF MENDELIAN DISORDERS

Although some inherited disorders of humans are due to the combined effects of multiple genes (multigenic disorders) or to the combined effects of genes and the environment (multifactorial disorders), a so-called Mendelian disorder is caused by a single defective allele. Over 3000 Mendelian disorders are known. They range from mild conditions such as red-green color blindness to life-threatening diseases such as cystic fibrosis. Because the defective allele can be either dominant or recessive and can reside on either an autosome or a sex chromosome (in particular, the X chromosome–very few genes reside on the small human Y chromosome), four types of Mendelian disorders are possible: autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive. Each type of disorder reveals itself through a distinctive pattern of inheritance in a family pedigree. Illustrated here are the patterns for three of the four types of Mendelian disorders.



Consider first the inheritance of an autosomal dominant Mendelian disorder. Many such disorders are expressed only in adulthood, including Huntington's disease, neurofibromatosis, and polycystic kidney disease. Shown in (a) are the equally probable genotypes and the phenotypes of the offspring of an affected father and an unaffected mother (or of an affected mother and an unaffected father). The genotype of the affected father can be either *DD* or *Dn*, where *n* is the nondefective recessive version of the defective dominant allele *D*. Because the father's having the genotype *DD* is the less typical and less interesting situation (all his offspring would be affected), it is assumed in (a) that the father has the genotype *Dn*. Because the mother is unaffected, her genotype must be *nn*. The equal segregation of chromosomes during meiosis implies that the offspring of such a mating can have one of two equally probable genotypes: *Dn* or *nn*. Therefore the probability of an offspring's being affected is 1/2. Note carefully, though, that only in the limit of an infinite number of offspring will the ratio of affected to unaffected offspring be equal to 1. Also shown in (a) is the pedigree of a family afflicted with hypercholesterolemia, a dominant disorder that causes excess levels of cholesterol in the blood. A thirty-year-old white male (II-4) suffered a myocardial infarction, a type of heart blockage, and was then found to test positively for hypercholesterolemia. Further tests indicated that his sister (II-1) and his four children (III-6, III-7, III-8, III-9) also had hypercholesterolemia. In addition, a family history revealed that the man's father (I-3) and uncle (I-1) both died of myocardial infarctions before reaching the age of fifty-five. Note that all of II-4's children are affected by the disorder, an outcome that is not inconsistent (although it may appear to be) with the probabilistic predictions based on the chromosome theory of heredity. Note also that the disease appears in all three generations of the pedigree; such a "vertical" pattern is characteristic of dominant disorders.

Shown in (b) is the inheritance of an autosomal recessive Mendelian disorder, examples of which include Tay-Sachs disease, cystic fibrosis, and sickle-cell anemia. Assume a typical situation: Both parents are carriers, or, in other words, are unaffected but have the genotype *Nd*, where *N* is the nondefective dominant version of *d*. The equal segregation of chromosomes during meiosis implies that the probability of an offspring's having the genotype *dd* and therefore of being affected is 1/4. In addition, the probability of an offspring's having the genotype *Nd* or *dN* (and of being a



carrier) is 1/2 and of having the genotype *NN* (and of being unaffected) is 1/4. Also shown in (b) is the pedigree of a family with an autosomal recessive Mendelian disorder. Only two individuals, both in the third generation (III-1 and III-4), are affected. All the other individuals listed are either carriers or unaffected. Since typically siblings in only a single generation are affected by a recessive Mendelian disorder, its inheritance pattern is referred to as horizontal.

Shown in (c) is the inheritance of an X-linked recessive Mendelian disorder. Such disorders include hemophilia, which is the result of a lack of an essential blood-clotting factor, and Duchenne muscular dystrophy, which causes progressive muscle weakness and death in early adulthood from respiratory problems. Again assume a typical situation: The mother is a carrier and therefore has the genotype X^dX^N, and the father is unaffected and therefore has the genotype X^NY. Any male offspring has a probability of 1/2 of being affected, and any female offspring has a probability of 1/2 of being a carrier. Also shown in (c) is a pedigree of a family with Duchenne muscular dystrophy. One son (II-2) and two daughters (II-1 and II-3) inherited the maternal X chromosome on which the defective allele resides. The son, possessing only one X chromosome, is affected. On the other hand, the daughters are unaffected carriers, but their sons (III-2, III-6, and III-7) inherited the defective allele. The pedigree illustrates the typical pattern of inheritance of an X-linked recessive disorder: transmission from an affected male through his daughters to his grandsons. Females can inherit the disease if the father is affected and the mother is either affected or a carrier.