mRNA isolated from a cell or tissue specimen with a radioactive or fluorescent marker and annealing this heterogeneous population of polynucleotides to a solid-phase substrate to which many different polynucleotides of known sequence are attached. The signals from the labeled cDNA strands bound to specific locations on the array are monitored, and the relative abundance of particular sequences is compared with that from a reference specimen. Using this approach, microarray patterns can be used as molecular fingerprints to diagnose a particular disease (i.e., type of malignancy and its susceptibility to treatment and prognosis) and to identify the genes whose expression increases or decreases in a specific disease state (i.e., identification of disease-modifying genes).

Many other applications of molecular medicine techniques are available in addition to those in infectious diseases and oncology. Molecular methods can be used to sort out genetic differences in metabolism that may modulate pharmacologic responses in a population of individuals (i.e., pharmacogenomics), address specific forensic issues such as paternity or criminal culpability, and approach epidemiologic analysis on a precise genetic basis.

Genes and Human Disease

Human genetic diseases can be divided into three broad categories: those caused by a mutation in a single gene (e.g., monogenic disorders, mendelian traits), those caused by mutations in more than one gene (e.g., polygenic disorders, complex disease traits), and those caused by chromosomal abnormalities (Table 1-2). In all three groups of disorders, environmental factors can contribute to the phenotypic expression of the disease by modulating gene expression or unmasking a biochemical abnormality that has no functional consequence in the absence of a stimulus or stress.

Classic monogenic disorders include sickle cell anemia, familial hypercholesterolemia, and cystic fibrosis. These genetic diseases can be exclusively produced by a single specific mutation (e.g., sickle cell anemia) or by any one of several mutations (e.g., familial hypercholesterolemia, cystic fibrosis) in a given family (i.e., Pauling paradigm). Some of these disorders evolved to protect the host. For example, sickle cell anemia evolved as protection against *Plasmodium falciparum* malaria, and cystic fibrosis developed as protection against cholera. Examples of polygenic disorders or complex disease traits include type 1 (insulin-dependent) diabetes mellitus, atherosclerotic cardiovascular disease, and essential hypertension. A common example of a chromosomal disorder is the presence of an extra chromosome 21 (i.e., trisomy 21).

TABLE 1-2 MOLECULAR BASIS OF MUTATIONS

TYPE	EXAMPLES
MONOGENIC DISORDERS	
Autosomal dominant	Polycystic kidney disease 1, neurofibromatosis 1
Autosomal recessive	β-Thalassemia, Gaucher's disease
X-linked	Hemophilia A, Emery-Dreifuss muscular dystrophy
One of multiple mutations	Familial hypercholesterolemia, cystic fibrosis
POLYGENIC DISORDERS	
Complex disease traits	Type 1 (insulin-dependent) diabetes, essential hypertension, atherosclerotic disease, cancer
CHROMOSOMAL ABNORMALITIES	
Deletions, duplications	Turner Syndrome (monosomy), Down Syndrome (Trisomy)

The overall frequency of monogenic disorders is about 1%. About 60% of these include polygenic disorders, which includes those with a genetic substrate that develops later in life. About 0.5% of monogenic disorders include chromosomal abnormalities. Chromosomal abnormalities are frequent causes of spontaneous abortion and malformations.

Contrary to the view held by early geneticists, few phenotypes are entirely defined by a single genetic locus. Monogenic disorders are comparatively uncommon; however, they are still useful as a means to understanding some basic principles of heredity. Three types of monogenic disorders occur: autosomal dominant, autosomal recessive, and X-linked. *Dominance* and *recessiveness* refer to the nature of the heritability of a genetic trait and correlate with the number of alleles affected at a given locus. If a mutation in a single allele determines the phenotype, the mutation is said to be dominant; that is, the heterozygous state conveys the clinical phenotype to the individual. If a mutation is necessary at both alleles to determine the phenotype, the mutation is said to be recessive; that is, only the homozygous state conveys the clinical phenotype to the individual. Dominant or recessive mutations can lead to a loss or a gain of function of the gene product. If the mutation is present on the X chromosome, it is defined as X-linked (which in males can, by definition, be viewed only as dominant); otherwise, it is autosomal.

The importance of identifying a potential genetic disease as inherited by one of these three mechanisms is that the disease must involve a single genomic abnormality that leads to an abnormality in a single protein. Classically identified genetic diseases are produced by mutations that affect coding (exonic) sequences. However, mutations in intronic and other untranslated regions of the genome occur that may disturb the function or expression of specific genes. Examples of diseases with these types of mutations include myotonic dystrophy and Friedreich ataxia.

An individual with a dominant monogenic disorder typically has one affected parent and a 50% chance of transmitting the mutation to his or her offspring. Men and women are equally likely to be affected and equally likely to transmit the trait to their offspring. The trait cannot be transmitted to offspring by two unaffected parents. In contrast, an individual with a recessive monogenic disorder typically has parents who are clinically normal. Affected parents, each heterozygous for the mutation, have a 25% chance of transmitting the clinical phenotype to their offspring but a 50% chance of transmitting the mutation to their offspring (i.e., producing an unaffected carrier).

Notwithstanding the clear heritability of common monogenic disorders (e.g., sickle cell anemia), the clinical expression of the disease in an individual with a phenotype expected to produce the disease may vary. *Variability in clinical expression* is defined as the range of phenotypic effects observed in individuals carrying a given mutation. *Penetrance* refers to a smaller subset of individuals with variable clinical expression of a mutation and is defined