as the proportion of individuals with a given genotype who exhibit any clinical phenotypic features of the disorder.

Three principal determinants of variability in clinical expression or incomplete penetrance of a given genetic disorder can occur: environmental factors, the effects of other genetic loci, and random chance. Environmental factors can modulate disease phenotype by altering gene expression in several ways, including acting on transcription factors (e.g., transcription factors that are sensitive to cell redox state, such as nuclear factor-κB) or on *cis*-elements in gene promoters (e.g., folate-dependent methylation of CpG-rich regions) and post-translationally modifying proteins (e.g., lysine oxidation). That other genes can modify the effects of disease-causing mutations is a reflection of the overlay of genetic diversity on primary disease phenotype. Numerous examples exist of the effects of these *disease-modifying genes* producing phenotypic variations among individuals with the identical primary disease-causing mutations (i.e., gene-gene interactions) and the effects of disease-modifying genes interacting with environmental determinants to alter phenotype further (i.e., gene-environment interactions). These interactions are important in polygenic diseases; gene-gene and gene-environment interactions can modify the phenotypic expression of the disease. Among patients with sickle cell disease, for example, some experience painful crises, others exhibit acute chest syndrome, and still other presentations include hemolytic crises.

Genetic disorders affecting a unique pool of DNA, mitochondrial DNA, have been identified. Mitochondrial DNA is is inherited only from the mother. Mutations in mitochondrial DNA can vary among mitochondria within a given cell and within a given individual (i.e., heteroplasmy). Examples of disorders of the mitochondrial genome are Kearns-Sayre syndrome and Leber hereditary optic neuropathy. The list of known mitochondrial genomic disorders is growing rapidly, and mitochondrial contributions to a large number of common polygenic disorders may also exist.

Molecular Medicine

A principal goal of molecular strategies is to restore normal gene function to individuals with genetic mutations. Methods to do so are currently primitive, and a number of obstacles must be surmounted for this approach to be successful.

Delivering a complete gene into a cell is not easy, and persistent expression of the new gene cannot be ensured because of the variability in its incorporation in the genome and the consequent variability in its regulated expression. Many approaches have been used, but none has been completely successful. They include the following: (1) packaging the cDNA in a viral vector, such as an attenuated adenovirus, and using the cell's ability to take up the virus as a means for the cDNA to gain access to the cell; (2) delivering the cDNA by means of a calcium phosphate–induced perturbation of the cell membrane; and (3) encapsulating the cDNA in a liposome that can fuse with the cell membrane and thereby deliver the cDNA.

After the cDNA has been successfully delivered to the cell of interest, the magnitude and durability of expression of the gene product are important variables. The magnitude of expression is determined by the number of copies of cDNA taken up by a cell and the extent of their incorporation in the genome of the cell. The durability of expression appears to depend partly on the antigenicity of the sequence and protein product.

Notwithstanding these technical limitations, gene therapy has been used to treat adenosine deaminase deficiency successfully, which suggests that the principle on which the treatment is based is reasonable. Clinical trials of gene therapy slowed considerably after unexpected deaths were widely reported in the scientific and lay media. Efforts in other genetic disorders and as a means to induce expression of a therapeutic protein (e.g., vascular endothelial cell growth factor to promote angiogenesis in ischemic tissue) are ongoing.

Understanding the molecular basis of disease leads naturally to the identification of unique disease targets. Examples of this principle have led to the development of novel therapies for diseases that have been difficult to treat. Imatinib, a tyrosine kinase inhibitor that is particularly effective at blocking the action of the BCR-ABL kinase, is effective for the treatment of chronic-phase chronic myelogenous leukemia. Monoclonal antibody to tumor necrosis factor-α (infliximab) and soluble tumor necrosis factor-α receptor (etanercept) are prime examples of *biologic modifiers* that are effective in the therapy of chronic inflammatory disorders, including inflammatory bowel disease and rheumatoid arthritis. This approach to molecular therapeutics is rapidly expanding and holds great promise for improving the therapeutic armamentarium for a variety of diseases.

Beyond cancer-related categories (e.g., DNA, RNA repair), gene expression arrays have identified additional interactions of regulatory pathways of clinical interest. The limitation of gene expression profiling using microarrays, which does not account for post-transcriptional and other post-translational modifications of protein-coding products, will likely be overcome by advances in proteomics. Such processes by signaling networks tend to amplify or attenuate gene expression on time scales lasting seconds to weeks. Much work remains to improve current knowledge about the pathways that initiate and promote tumors. The basic pathways and nodal points of regulation will be identified for rational drug design and targets from mechanistic insights gleaned from expression profiling of cultured cell lines, from small animal models of human disease, and from human samples. Although accounting for tissue heterogeneity and variation among different cell types, the new systems' approach for incorporating genomic and computational research appears particularly promising for deciphering the pathways that promote tumorigenesis. Biologists and clinicians will use information derived from these tools to understand the events that promote survival, proangiogenesis, and immune escape, all of which may confer metastatic potential and progression.

What potential diagnostic tools are available to establish genetic determinants of drug response? Genome-wide approaches from the Human Genome Project in combination with microarrays, proteomic analysis, and bioinformatics will identify multiple genes encoding drug targets (e.g., receptors). Similar high-throughput screening should provide insights into the predisposition to adverse effects or outcomes from treatments that are linked to genetic polymorphisms.