SCIENCE

EDITORIAL

Molecular Advances in Diseases

Long before the current era of molecular biology a scientist named Garrod recognized that certain diseases were not caused by infection but were rather "inborn errors of metabolism." Today there is no doubt that Garrod was right, and the advances of modern biology have allowed us to identify the precise genes that cause a number of inherited diseases. In this issue, Katrina Kelner and Pamela Hines have assembled eight articles that are illustrative of the modern understanding of genetic disease and of future therapies. In addition, Jean Marx has edited a biotech special report that investigates the role of biotechnology in combating disease.

Gibbons' news report on the next generation of biotech products describes three molecular approaches that companies are pursuing. These include blocking the genetic code, using novel classes of molecules to block receptors, and designing organic molecules to interfere with signaling pathways. Although the commercial feasibility of these products has not been determined, Hoffman reports that Massachusetts is hoping to tie its economic future to the success of these approaches. Moffat points out that plants are another source of new biotech products that have potential application in therapeutic and diagnostic medicine. The final news report by Kolberg describes methods used to alter specific genes in animals in order to create disease models and stresses the importance of animal models for testing gene therapy.

In the articles section, Collins discusses the extraordinarily important developments in a prevalent molecular disease, cystic fibrosis. There had been some understanding of the biochemical dysfunction in cystic fibrosis, but no animal model. As a result of cloning the gene, new approaches to therapy for cystic fibrosis are now emerging. Another genetic disease, epidermolysis bullosa, is discussed by Epstein. He identifies epidermolysis bullosa with other hereditary diseases of the skin and also describes its cause as a defect in the cytoskeletal filament network. Retinitis pigmentosa, also an inherited disease, affects the human visual system with an estimated prevalence of approximately 1 in 3000 newborns. Mutations in two genes encoding transmembrane proteins of the rod outer segment disc as well as some other genes are described as the causes of this disease by Humphries, Kenna, and Farrar.

Alzheimer's disease, which exhibits a number of bewildering traits that do not easily fit into one theory, is described by Kosik. He discusses the precipitation of protein fragments and the possible causes. Although all the causes are not known, some are attributable to specific mutants in metabolic pathways. A genetic phenomenon, triplet repeat mutation, that causes and affects the severity of certain diseases, is described by Caskey, Pizzuti, Fu, Fenwick, and Nelson. Diseases caused by this phenomenon include fragile X, which causes mental retardation; spine and bulbar muscular atrophy, which involves muscle weakness and neural degeneration; and myotonic dystrophy, which is characterized by cardiac arrhythmias, cataracts, and male infertility. All of these seem to have similar mechanisms involving amplification of a short sequence of DNA. This mechanism is now easily recognizable and may lead to the unraveling of other molecular diseases.

Gaucher disease, discussed by Beutler, is a disease with defects of glucose cerebroside formation in which therapy by intravenous infusion of glucocerebrosidase, an enzyme, can be a somewhat effective treatment. Malignant hyperthermia, described by MacLennan and Phillips, is a disease of rare occurrence but dramatic impact. Individuals who otherwise seem healthy, when exposed to anesthesia, suddenly experience muscle rigidity, hypermetabolism, high fever, and often death. Knowledge of the molecular biology has made it possible to reduce the morbidity drastically (by 70%). Gene therapy, as discussed by Anderson, is now proceeding with increasing efficacy and rapidity and therefore will certainly be a treatment of choice for those with the money to afford it.

The finding that some diseases are inherited and hence not preventable by loving care or good antibiotics raises ethical and societal concerns in regard to the methods of therapy and their effects on the germline. But the simplistic solution that the sins of commission are worse than the sins of omission will not suffice. The question of how to correct inherited diseases is worthy of deep ethical and scientific consideration and will probably require some legislation and financial subsidies to assure fairness, but the research should continue. Our current drug therapies and general health are preserving some genetic defects that would have been weeded out in a crueler and less friendly world and will require the remedies offered by kinder and gentler molecular medicine.

Daniel E. Koshland, Jr.

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