plenary session I: friday, march 10

Distinguished Speakers Symposium

The molecular genetics of muscular dystrophy. L.M. Kunkel. Howard Hughes Medical Institute and Children's Hospital, Boston, MA.

The muscular dystrophies are progressive disorders of striated muscle leading to breakdown of muscle integrity. Underlying this clinical presentation there is considerable genetic heterogeneity, with the X-chromosomal recessive Duchenne and Becker forms comprising the majority of patients, and the related limb girdle muscular dystrophies (LGMD) being caused by an additional 10 genetic loci. Much has been learned over the last 10 years about the molecular defects associated with the muscular dystrophies, beginning with the identification of dystrophin as the protein altered in Duchenne/Becker muscular dystrophy. Dystrophin has since been shown to be part of a complex of proteins at the muscle cell membrane known as the dystrophin associated protein complex (DAP). Five other protein members of this complex are themselves encoded by genes that are disrupted in LGMD patients. The exact mechanism by which the muscle cell undergoes degeneration when this complex is disturbed is unknown. Recently, filamin-2 (FLN2) has been shown to be part of the sarcoglycan subcomplex and the sequence homology to FLN1 of non-muscle tissues and FLN1 known function implies a previously unrecognized signaling role for the sarcoglycans. The characterization of the DAP complex has led to improved diagnosis of the dystrophies yet to date there is no known way to halt the muscle cell degeneration when this complex is perturbed. Dystrophin replacement can be completely corrective in animal models. Both gene therapy and cell-based therapies have been tested. One very promising avenue of treatment involves stem cells isolated from muscle and their systemic delivery to diseased tissues. In a bone marrow transplantation model of cell delivery, these stem cells can be injected into the tail veins of dystrophin-deficient mice, and within 21 days can be found to reconstitute the bone marrow of the mice. In addition, upwards of 10% of muscle fiber are found to be producing absent dystrophin. The new millennium should witness improved understanding of the dystrophies and the advent of rational therapies.

Beyond the Human Genome Project: Genetics and Ethics, Human Nature and Society. K.T. FitzGerald. Loyola Univ. Med. Ctr., Maywood, IL.

The Human Genome Project is a striking example of the rapid increase of genetic information inundating scientific journals and also the media. Though this information may result in marvelous new possibilities for diagnosis and treatment, this genetic information also raises many quandries concerning how this information will be used and to what purpose. Even the seemingly simple purpose of using this information to uncover the genetic basis of certain diseases becomes problematic. The problems arise when new genetic information threatens to unravel the very concepts of health and disease being employed in medicine and in society. Concepts of what is "normal" for human beings are often now challenged by interested parties wielding the latest research. How then can we make good use of this new information? In order to move forward, we need to step back and assess the adequacy of our concepts of health and disease, and our concepts of human nature. What is needed are concepts of human nature that can weave the new threads of genetic information into the rich tapestry of knowledge we already possess about who we are and how we desire to live together.

Genetic mechanisms of cancer development. A.G. Knudson. Fox Chase Cancer Center, Philadelphia, PA

There are probably 50 or more hereditary forms of cancer, for some 25 of which the responsible gene has been cloned. Some of the genes are oncogenes or DNA mismatch repair genes, but most are tumor suppressor (*ts*) genes. These *ts* genes are mutant in at least some non-hereditary cases of tumors corresponding to those found in the hereditary forms. The tumors in both forms are typically "2 hit" lesions; i.e., both alleles of the gene in question are mutant or absent.

Two of these genes, *RB1* and *TP53*, or genes closely related to them physiologically, are mutated in a wide variety of cancers, making it appear that they normally play central roles in protecting against cancer, one by regulating the birth rate of cancer cells, and the other, the death rate. Diverse tumors are found in the hereditary forms of each, but the list of typical tumors does not include others that show a high rate of somatic mutation in these two genes.

Ten of the cloned genes are mutated in the syndromes known as phakomatoses, each of which gives rise clinically to "2 hit" benign tumors or harmartomas. Most such lesions do not progress to malignancy, but, when they do, they often show mutations in the *RB1* or *TP53* pathway. On the other hand, the tumors that are typically found in hereditary retinoblastoma or the Li-Fraumeni syndrome, are not usual features of the phakomatoses. The phakomatoses genes are all active in intracellular signal transduction.

Most carcinomas show more genetic changes than do the tumors of childhood, suggesting that the opportunities for cancer prevention are greater in adults and for treatment, in children.