Am. J. Hum. Genet. 66:1190–1191, 2000

1999 ASHG AWARD FOR EXCELLENCE IN EDUCATION
Some Future Directions in Medical Genetics

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Working in human and medical genetics in the last half of the 20th century has been a privilege. Our field has evolved from Cinderella status to become the queen of the biomedical sciences. The honor of receiving the "Excellence in Education" award of the American Society of Human Genetics is therefore particularly gratifying. I thank my many colleagues, postdoctoral fellows, and collaborators who have made my work possible. Particularly, I call attention to Friedrich Vogel's major role in writing our book on human genetics.

Pathogenesis of Genetic Disease

As medical geneticists, we can contribute to an understanding of the pathogenic mechanisms of genetically influenced disease. The public supports such research in the hope of prevention and treatment. Where will the desired answers come from? In monogenic diseases, positional cloning has identified various mutations in many different genes. Often, we know how a mutant gene product causes disease, such as in the various enzyme deficiencies and protein defects. In an increasing number of examples, however, the gene products identified by positional cloning are completely novel. We do not know their function, and we have few or no clues how a mutant gene causes disease. Examples are Huntington disease, Friedreich ataxia, Werner syndrome, and many others. How does an abnormal helicase produce findings suggestive of premature aging, as in Werner syndrome? We need to learn much more about the mechanisms of pathogenesis, i.e., the pathways that lead from the altered gene to the phenotype. Many monogenic diseases, despite identical nucleotide errors in the same gene, such as in adult Gaucher disease, exhibit low penetrance, but the responsible mechanism remains unknown.

One approach needing more attention is the study of modifying genes. A definite example of genetic modification is the apolipoprotein E polymorphism that alters the expression of late-onset Alzheimer disease. E_4 heterozygotes and, particularly, E_4 homozygotes have a higher risk of being affected with Alzheimer disease. Another example is a small deletion in the CCR5 coreceptor for the HIV virus that completely protects against HIV infection when homozygous and increases the time period between HIV infection and clinical AIDS in heterozygotes. The exciting vista of these examples is that understanding of the mechanisms of action of such modifiers may provide clues towards preventive or therapeutic measures. Thus, once it is understood that the HIV virus requires the CCR5 receptor to be infective, therapeutic and preventive agents can be devised that use this knowledge.

Search for modifying genes also applies to the pathogenesis of the various complex diseases where multiple genes are operative. So far, genomic mapping studies in these conditions have often given nonreproducible results. Excepting the uncommon monogenic subtypes, few, if any, genes or gene products have been definitely identified by this approach alone. Markers such as the common single-nucleotide polymorphisms (SNPs) that are in linkage disequilibrium with a disease locus may lead to disease-gene identification, and extensive efforts are underway to identify SNPs in various complex diseases as well as in traits of pharmacogenomic interest. The term "phenogenetics" has been used to denote the genetic study of phenotypic expression and may be useful to call attention to studies on modifying genes.

However, identification of the involved genes will not be enough. We need more attention to gene-gene interaction, to epistatic factors, and to definition of the specific environmental factors in gene-environmental interaction. The role of developmental changes at the embryonic-fetal level needs attention. For late-onset diseases, the mechanisms of the aging in different organs and its role in pathogenesis of disease requires better understanding.

Stochastic or random factors may play a role in disease pathogenesis. Why is concordance for complex disease in identical twins often only in the 40%–70% range, even though such twins share all of their germinal genes and usually have the same intrauterine and postnatal environment. Do somatic mutations play a role? Is the frequent lack of MZ-twin concordance really environmental? Are there other poorly understood epigenetic factors? Does chance ever play a role, particularly during development?

The term "phenomics" has been used to denote the

Received January 19, 2000; accepted for publication January 21, 2000; electronically published March 15, 2000.

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0002-9297/2000/6604-0003$02.00

broad study of the phenotype that must be carried out in conjunction with genomics. "Proteomics," i.e., study of proteins and their expression during developmental, physiologic, and pathologic processes using many new techniques, is an important part of phenomics.

Many scientific approaches are required to understand the pathway from genotype to phenotype. Fields of genetics that are involved include molecular genetics, biochemical genetics, pharmacogenetics, clinical genetics, genetics of aging, and statistical and epidemiologic genetics. We will need the help of specialists in many areas. Biochemists, cellular and system physiologists, pathologists, and pharmacologists will need to provide data and insights. There is need for broadly trained individuals in medical genetics who, by using a variety of current information from various computerized databases, can make sense of the large amounts of emerging data. Nick Schork suggested that we need a new kind of researcher—an "armchair" scientist who can excel in this activity. However, skill in informatics will not be enough. We need creative minds that are able to integrate the many data into meaningful patterns to suggest promising new studies to understand disease. Broadly trained medical geneticists are ideal candidates for these activities.

Implications for Training in Medical Genetics

Renewed attention to biochemistry and physiology will be important, so that team work will be easier. Study of modifying genes in simpler organisms such as mice and fruit flies will be useful. Laboratory workers need to learn about the principles of statistics, population genetics, and epidemiology to appreciate the power and limitations of quantitative approaches. Quantitatively trained geneticists will need exposure to the biologic realities posed by the problems they work on.

Clinical investigators and physician-scientists who work on problems of genetically influenced disease are either medical geneticists or work with geneticists. Intermediate phenotypes (i.e., those phenotypes that are closer to gene action than the diagnostic label of the disease) often need to be identified. As an example, the study of hyperlipidemia, instead of coronary artery disease, has been useful in starting to dissect the genetic etiology of arteriosclerosis. Since large numbers of patients and normal controls are often required for association studies (such as with SNPs), the logistical arrangements and problems of working in a consortium with large numbers of patients in different institutions will need to be part of training young investigators. Ph.D. scientists in addition to in depth research require broader training as a basis for work in disease research. Summer courses in medical and clinical genetics specifically directed at Ph.D. geneticists are a possible solution.

Public Health Genetics

A new area of genetic education is appearing. An increasing number of schools of public health are initiating programs of public health genetics. At the University of Washington, the program is established within the framework of law, ethics, and public policy to emphasize its concern for the ethical, legal, and social aspects of human genetics. The program trains—usually at the Master's level, at this point, and aiming at Ph.D. programs later—professionals to work in public health departments, screening programs, government and legislative agencies of various sorts, policy analysis, law, bioethics, and, to some extent, as genetic counselors, public health nurses, and genetic epidemiologists.

The institution of these programs raises a variety of questions. For instance, how do we educate students without a scientific background in the science of genetics? This is difficult and needs experimentation.

Public health genetics programs hopefully will provide a site for scholarly research in the ethical, legal, and social problems of genetics. This aspect has intense public interest. Public health genetics programs are an ideal place where difficult problems could be researched in a university environment in collaboration with various social science and other departments. Such work, hopefully, will provide empirical data of various sorts.

U.S. Health Care System and Medical Genetics

The future organization of our complex health care system and its regulation will be an important factor in personnel requirements in medical genetics. There are many problems. Over 40 million people are uninsured. How can we provide appropriate genetic services to this underserved population, and how should that be done? Health maintenance organizations (HMOs) are here to stay for some time. To reduce costs, these organizations utilize cost-effectiveness analysis to define the needs for genetic services. A likely outcome is increasing utilization of genetic counselors, rather than of medical geneticists in HMO settings, which is already happening in cancer genetics. There is likely to be more patient education in matters of genetics with attention to prevention—a welcome development. The specific organization of various genetic services and the role of genetics in medical care is difficult to predict at this time and will depend on scientific developments and how health care in the U.S.A. will be administered in the future. There is no question, however, that our field of science and practice will play an important role in the medicine of the future.