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Relationship Between Medical Genetics and Public Health: Changing the Paradigm of Disease Prevention and the Definition of a Genetic Disease

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Over the past decade, medical genetics has emerged as an important and powerful medical specialty with increasing appreciation of its role and function among the medical specialties. This emergence is related to a great extent to the progress in the Human Genome Project which promises wide-ranging applications in the diagnosis, treatment and prevention of human diseases [Hoffman, 1994]. Nevertheless, discussions about the role of genetics in preventive medicine and public health rightfully lead to ethical, legal and social concerns about general applicability of genetic testing in the population [Garver, 1994; Holtzman, 1989]. The interpretation of the word *prevention* in the context of genetic diseases leads to the unavoidable discussions of genetic engineering, prenatal diagnosis and selective termination, as well as broader concerns about discrimination in health care coverage, employment and in society.

Figure 1 shows the classical public health view of disease prevention when applied to infectious and environmental agents. Primary prevention is classically thought of as the interruption of transmission of infectious agents or avoidance of exposure to environmental agents in the population through education, behavior modification, immunizations, and environmental measures (e.g., human immunodeficiency virus [HIV] infection or cigarette smoking). Secondary prevention is thought of as the interruption of clinical disease after the acquisition of the infectious agent or exposure to the environmental agent. In the case of HIV, this entails steps to prevent or delay the onset of the acquired immunodeficiency syndrome (AIDS) by using drugs and other medical, nutritional and psychosocial measures. Tertiary prevention is thought of as the prevention of complications of the disease after it occurs [Khoury et al., 1996]. For example, this applies to the prevention of opportunistic infections (OI) in AIDS through appropriate prophylactic medical guidelines. The prevention of human disease by preventing exposures and infectious agents has been the force driving programs in public health and preventive medicine [Khoury et al., 1996].

When it comes to genetic diseases, as shown in Figure 1, a typical reaction of medical and public health professionals is that the classical public health model does not work since peoples' genotypes are not changeable (except, of course, with genetic engineering), and that such a prevention model could lead to eugenic consequences (i.e., preventing the birth of people with specific genotypes). This may lead to reasonable concerns about public health applications of genetic technologies and genetic tests.

Here, I argue that in order for medical genetics and public health to interact successfully, the public health community needs to change the classical disease prevention paradigm and the medical genetics community needs to change the definition of and the approach to the label "genetic disease."

Let us use the word genotype for both disease genes and disease-susceptibility genes. The first group includes genotypes that have high penetrance for the development of clinical disease (e.g., homozygosity for the sickle cell mutation, the cystic fibrosis gene mutations, and heterozygosity for BRCA1 mutations). The second group includes genotypes that have low penetrance for clinical disease development and some could even be considered normal variants (i.e., genetic risk factors such as HLA-B27 and ankylosing spondylitis, and apolipoprotein E-E4 allele and Alzheimer disease). For example, inheritance of the sickle cell mutation in the homozygous phase leads to sickle cell anemia. In turn, various medical problems and complications arise as a result of sickle cell disease, including strokes and pneumococcal sepsis. Certain BRCA1 mutations lead to the development of breast and ovarian cancers which lead to various medical complications including metastasis and psychosocial complications.

Here one can ask two simple questions: what is prevention in the context of genetic conditions? Clearly, primary prevention refers to the prevention of the disease entity for which the genotype is an important component. Primary prevention can occur by interrupting the environmental cofactors that interact with peoples' genotypes and/or by using gene therapy (Fig. 1). Primary prevention does not and should not refer to the

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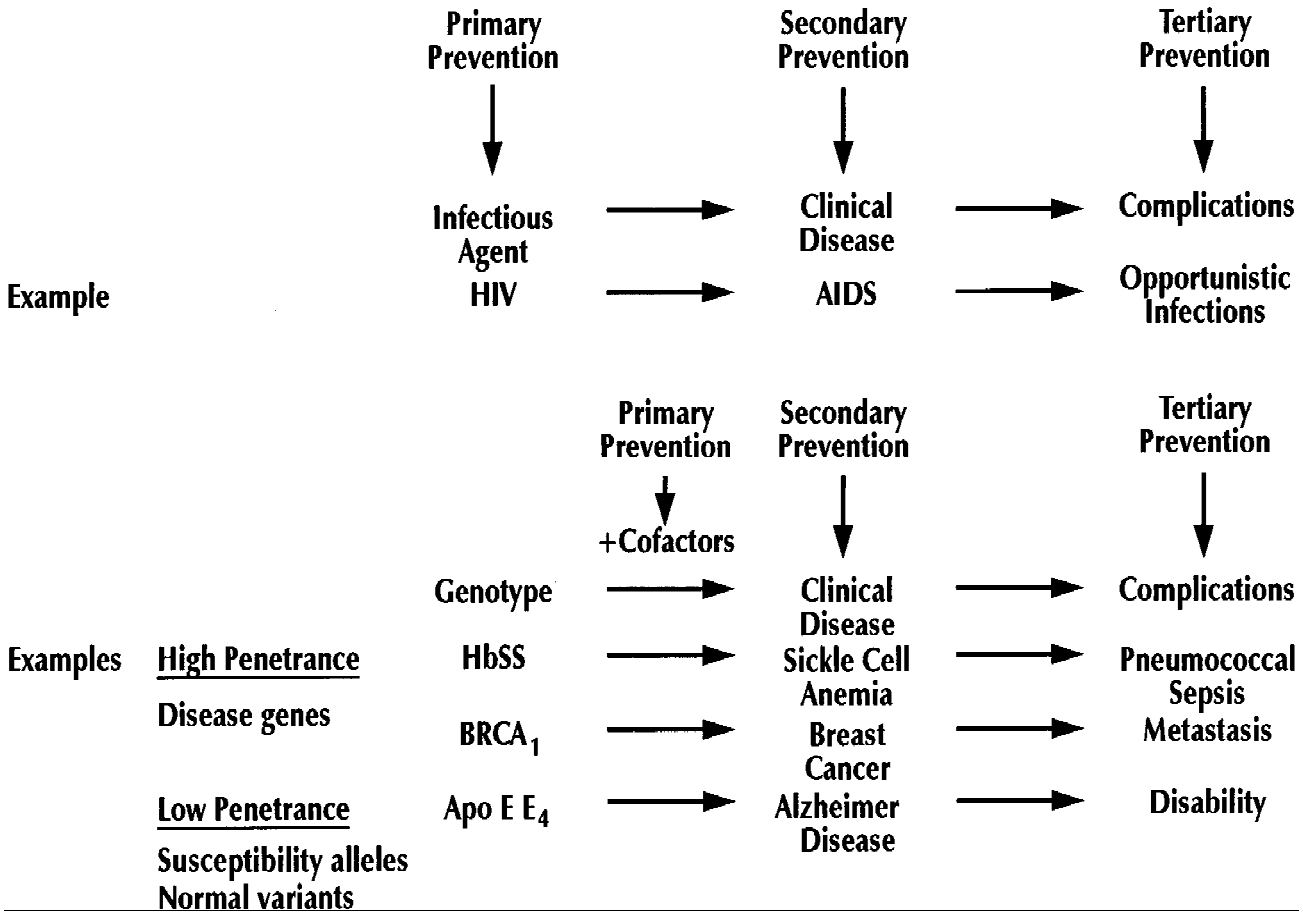

Fig. 1. Paradigms of disease prevention for infectious diseases and in medical genetics: HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; HbSS, homozygous sickle hemoglobin.

prevention of the genotypes per se (i.e., prevention of births of individuals with specific genotypes). While we all recognize that couples make informed reproductive decisions on the basis of carrier testing and prenatal diagnosis, such individual decisions should not be confused with disease prevention as discussed in the realm of public health. This distinction between phenotypic and genotypic prevention has been alluded to by Juengst [1995].

The second question is: what is a genetic condition after all? Geneticists often make a distinction between single gene disorders and susceptibility genes that are risk factors along with other genes and environmental exposures in disease development. This distinction is quantitative rather than qualitative as embodied in the concept of penetrance of the genotype. As a matter of fact, the distinction tends to fade when one realizes that all human disease is the result of the interactions between our genotypes and the environment broadly defined. Even the classical single gene metabolic disorders do involve nutritional interaction between the enzyme deficiency and the dietary exposure to one or more chemicals (e.g., phenylalanine and phenylalanine hydroxylase deficiency, iron and the hereditary hemochromatosis homozygous genotype). As Rothman puts it "it is easy to show that 100% of any disease is environmentally determined and 100% is genetically determined as well. Any other view is based on a naive view of causation" [Rothman, 1986]. Perhaps, the wide range of penetrance with respect to clinical disease could be due, in part, to the variations in the prevalence of the interacting cofactors (other genes and modifiable risk factors). The fact that there is universal phenylalanine exposure in the diet of newborn infants, leads to a high penetrance for those who inherit the phenylalanine hydroxylase deficiency (i.e., mental retardation).

This analysis leads to two simple clarifications: (1) primary prevention of human disease in the context of medical genetics refers to the prevention of the disease entity for which the gene or genes in question play a role. How can that occur? While gene therapy may become appropriate to correct certain deficient gene products leading to human disease, primary prevention of many multifactorial human disease will entail understanding and interruption of the environmental cofactors among individuals who inherit genetic susceptibility (polymorphisms or disease mutations). Phenylalanine and iron in the diet have been mentioned for PKU and hereditary hemochromatosis. However, for most human genes including BRCA1 (in relation to breast cancer), and Apo E-E4 (in relation to Alzheimer disease), such cofactors are still poorly understood and a

lot of epidemiologic work needs to be done in various populations in order to target prevention; and (2) we need to refine our approach to defining and labeling genetic diseases. If we accept the basic premise that genes cause human diseases, it may make a lot of sense to stop labeling a disease as genetic or not. For example, this approach will lead to labeling hereditary hemochromatosis as an iron overload disorder resulting from the interaction between an inherited abnormality in iron transport and iron intake. Using the same approach, breast cancer in some individuals could result from the interaction between an inherited mutation in the BRCA1 gene and yet to be described cofactor(s). The parallel between genetic diseases and infectious disease is such that the concept of prevention and control that may be acceptable in the context of infectious agents is totally unacceptable in the context of genetic conditions. As Francis Collins puts it simply: "we're all at risk for something" [Beardsley, 1996]. This ultimate and powerful realization could be the driving force in medicine, public health and society at large to accept once and for all our genetic makeup and direct our focus and attention to the prevention of human disease and suffering by targeting our disease prevention strategies to modifiable risk factors (e.g., dietary factors) according to each and everyone's unique biologic susceptibilities. Such a realization could also be the engine that drives the much needed reform in our health care system.

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