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Genetic Screening: Implications for Preventive Medicine

Genetic screening is a search for persons in a population who possess certain genotypes: that are associated with existing disease or predispose to future disease; that may lead to disease in their descendants; or that produce other variations of interest but not known to be associated with disease.[1]

This concept is not quite encompassed in an earlier and well-respected document on screening for disease.[2] It is obviously relevant to citizens living in industrialized societies who have benefited from traditional practices in public health.[3] It has become a conventional public health exercise to screen bloods of newborns for the hyperphenylalanimenias, the tyrosinemias, the amino acidopathies in general, the galactosemias, and the aberrations of thyroid hormone biosynthesis; and to screen urines for disorders of amino acid or monosaccharide metabolism and transport. Screening of young adults to initiate genetic counseling for indications of Tay-Sachs, β thalassemia, and sickle cell heterozygosity has also become a common practice in the relevant high-risk ethnic communities. Screening to identify persons with variant phenotypes, such as α_1-antitrypsin deficiency, has become a form of epidemiologic research to discover the natural history of the variant.

Each of the screening modes presupposes that a risk to health can be identified and that something can be done to prevent disease or to understand better the predisposition to disease. Because disease is a biological phenomenon with particular significance for humans, it is worthwhile to consider briefly the nature of disease from a biological viewpoint and the particular relevance of genetic screening in a modern world.

Health reflects biological homeostasis within the limits of an optimal steady state; accordingly, disease can be considered as a deviant biological state with outcomes expressed as morbidity and mortality. The biological impact of disease is reflected in measures of viability, development (morphologic and cognitive), fertility, and longevity. The primary "cause" of disease is, at one extreme, an extrinsic event that disturbs the steady state; at the other, an intrinsic event that alters components of the steady state and modifies its response to disturbing events. That is to say, phenotype is always the product of interactions between nature (genotype) and nurture (experience). The case is put succinctly in the aphorism: "genes propose; experiences dispose."*

Public health has made remarkable contributions to control of the aberrant (extrinsic) experience. Morbidity and mortality related to pathogens and deviant nutrition are greatly reduced in 20th century industrial societies, relative to earlier times (see for example a recent account of 18th Century medical practice.[4] It follows that the heritability** of human disease has probably increased relative to earlier times. That is clearly the case for the phenotype of rickets in childhood;[5] it is also

*The aphorism is attributed to Barton Childs.

**Heritability in the broad sense is the ratio of phenotypic variability due to genotype over total variability of phenotype (the latter = variability derived from environment plus variability due to genotype).

implied for anemia, as an article by Grover and colleagues in this month's issue of the Journal[6] illustrates. Thus the modern goal of disease prevention through public health practices requires awareness not only of potential harm in the environment but also of risk (susceptibility) in individuals within populations.

Screening for disease is a traditional public health activity. Its objective is the presumptive identification of disease or defect by the application of tests, examination, and other procedures that can be applied rapidly. It attempts to sort out apparently well persons who probably have a disease from those who probably do not.[2] The specific goals of *genetic screening* are to: 1) identify persons, who will benefit from medical interventions that neutralize morbid expression of mutant genes; 2) identify persons who, by virtue of their own asymptomatic genotype, may harm offspring when the mutation is passed on and who may avoid such harm after counseling about reproductive options; and 3) identify variant phenotypes in populations and, through appropriate studies, describe their biological effects. Grover, *et al*, encompassed each of these three rationales while screening newborn infants for sickle hemoglobin (HbS).[6]

The authors conducted and analyzed a program in New York City over a 12-month period; 106,565 blood samples were screened for a phenotype (HbS) resulting from mutation at the β-globin locus on chromosome 11p12. They employed an electrophoretic method for delineation of S globin in whole blood collected on filter paper; their program provided specific diagnosis, follow-up of infants, and counseling for their families. The importance of an integrated program that provided screening and the additional components cannot be emphasized sufficiently. Absence of a comprehensive programmatic approach in any form of genetic or newborn screening is bound to generate unwanted problems.[1]

Grover and coworkers identified 141 infants at risk for serious disease associated with an HbS phenotype (SS, SC and Sβthal genotypes). They retrieved 131 patients and initiated follow-up observations. While it is still too early to discern whether early diagnosis and prospective management consistently altered the natural history of the disease in these infants, the program is of great interest because of the opportunity it offers to observe the natural history of HbS disease from birth in a large cohort. Students of HbS-associated disease know that knowledge of its early natural history is still sparse; that is why a national multicenter study (to which the New York City program will contribute) is in progress—to generate knowledge. It is a bizarre anomaly of American society that screening of heterozygotes for HbS-associated disease was vigorously promoted not so long ago in the absence of such basic knowledge; and that cutbacks in funding now jeopardize efforts to generate the required knowledge. This seems to be the wrong time to handicap the attainment of facts when their attached values need to be examined in an objective manner. Those who advocated and voted funds to support the New York City program deserve congratulations; anyone who would do less for an issue relevant to 10 per cent of the nation's population must be ignorant of the issues or guided by warped priorities.

Newborn HbS screening is considered by some to be a potential means of reducing the frequency of HbS-associated disease in the population. Early diagnosis of a proband may influence reproductive behavior within a family, but it will have a relatively small effect on prevalence of the phenotype in the population. The actual reduction in incidence is determined by the formula $n/4 - [1-(\alpha)^n]/n/4$ where n is the number of children in the sibship and α is the probability of any particular child being normal. For a recessively inherited disease with average sibship size of two, the reduction of incidence is only about 12.5 per cent. A major impact on incidence can be achieved only through primary identification of heterozygotes and counseling before reproductive activity begins.

American communities at risk for HbS disease, for various reasons, have been only modestly accepting of heterozygote screening and midtrimester fetal diagnosis with termination of the affected pregnancy. In this respect, attitudes and behavior are rather different from those in communities at risk for thalassemia-associated disease. It is worth noting that heterozygote screening and fetal diagnosis have not only profoundly reduced mutation impact in several thalassemia communities, but have also encouraged families at specific risk to have healthy offspring.[7,8]

The reliability of screening methodology is always a matter of concern. The need for tests with high specificity, sensitivity, and predictive value is a matter of record in genetic screening as it is in any form of medical screening. Grover, *et al*, provide interesting confirmation of the excellence of their screening test. The number of heterozygous (AS) infants found (n = 3,473) permits an estimate of HbS gene frequency; the estimate agrees closely (yet with interpretable deviation) with the predicted frequency of genotype derived from demographic data.

The heterozygous infants identified by screening in the New York program have, of course, not yet been counseled. Nonetheless, there is an important issue to be decided. Heterozygotes are entitled to the information about their personal genotypes; it will be relevant during the upcoming reproductive interval in their lives. Clearly, a mechanism must be developed that can link data obtained by screening in the newborn period to the individuals from which it was obtained when they enter the fertile period of their lives. In this regard, a dedicated register, such as that described in a different context (maternal hyperphenylalaninemia), in the December 1982 issue of the Journal,[9] might be a useful adjunct to the screening program.

Delineation of heterozygosity in general will become increasingly relevant not only for reproductive counseling but also for health maintenance in individuals. Numerous diseases of mature life have an antecedant risk in genotype.[10] Since genes propose, it is pertinent to know what experiences dispose and to neutralize the potentially harmful expression of a particular genotype by modifying the experience; this is a medical strategy of disease prevention. There are specific forms of atherosclerosis, of idiosyncratic response to drugs, and of response to infection, with genetic predisposition, to mention but three broad categories. Genetic screening in such situations could become a powerful

tool to anticipate intrinsic risk for unhealthy longevity just as it is now a tool to prevent certain diseases of early life. That is why the genetic screening program in New York City is such an interesting "experiment." It is generating knowledge and expertise which, when fully appreciated, will transcend its original impetus from HbS-associated disease.

CHARLES R. SCRIVER, MD, CM, FRSC

Address reprint requests to Dr. Charles R. Scriver, Director, deBelle Laboratory, McGill University-Montreal Children's Hospital Research Institute, 2300 Tupper Street, Montreal, Quebec H3H 1P3.

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Long-Term Follow-Up Is a Problem

In this issue of the Journal, Nash, *et al,* report on the difficulties of conducting the national cooperative Diethylstilbestrol-Adenosis (DESAD) Project.[1] Their experience provides yet another example of the problems we face in conducting medical follow-up and epidemiologic studies in this country when many years intervene between exposure and disease. Despite the allocation of tremendous funds to medical care and the elegance of our technology, linking events in the life history of the individual in order to advance medical science is usually difficult and often impractical.

It is not only research on the late effects of drug therapies that suffers from the difficulties experienced in the DESAD Project. Unless they can be performed within closed medical care systems, or within population-based medical information systems, virtually all long-term follow-up studies are subject to some of the difficulties faced by the DESAD investigators, especially if events and outcomes other than mortality are at issue.

The barriers to long-term studies come to national attention only indirectly, as in the deliberations of the Privacy Protection Study Commission established by the Privacy Act of 1974.[2] The Commission was charged with surveying information systems from the standpoint of privacy and confidentiality and recommending to the President and the Congress changes in legislation designed to bring into better balance the information needs of society and the privacy of the individual. Perhaps the Congress recognized that the Privacy Act of 1974, having been hastily drafted in the wake of Watergate, might well be imperfect and need amendment. Although abuses arising from medical research seem not to have been any part of the driving force leading to their enactment, the Privacy Act and the later Tax Reform Act of 1976[3] have had a chilling effect on medical research both directly, in their restriction of access to federal record systems, and indirectly, through their ripple effects in state legislatures and private institutions.[4] The Commission took seriously its charge to balance public and private interest and, if enacted, its 1977 recommendations for modifications in the Act[5] would ameliorate many of the difficulties that beset the medical investigator. Unfortunately, the Privacy Act remains essentially unchanged even now, five years later.

The Tax Reform Act, on the other hand, has been modified to provide medical investigators with access to the taxpayers' address file of the Internal Revenue Service (IRS), but only through the National Institute for Occupational Safety and Health (NIOSH) ". . . for the purpose of locating individuals who are, or may have been, exposed to occupational hazards in order to determine the status of their health or to inform them of the possible need for medical care and treatment."[6] Later this "NIOSH window" was widened to admit individuals who may have been exposed to occupational hazards during active military service.[7] The wording of these amendments is quite restrictive, even for research on occupational hazards, and there remains an urgent need to modify the Internal Revenue Code further so that qualified medical investigators working under approved protocols may have access to the filing address and date of filing.

Two major sources of mortality information—the Social Security Administration (SSA) files and the Veterans Administration (VA) files—were greatly impaired by the 1981 tax bill that curtailed eligibility for the lump-sum death benefit programs of SSA, VA, and other agencies beginning October 1, 1981.[8] Had the National Death Index not been put in place by the National Center for Health Statistics (NCHS)[9] before that curtailment took place, we would have no truly national source of mortality follow-up after 1981.