Simultaneous Assessment of Genetic and Occupational Risk Factors

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Genetic factors rarely have been considered in studies of occupational risks. This leaves unresolved many questions of differential disease distribution in similarly exposed groups. In this analysis the medical and epidemiologic literature has been surveyed and the methods for assessing genetic and occupational risks in the same study have been identified and critiqued. Five major methodologic approaches have been identified: (1) adjustment for race, ethnicity, and sex; (2) case studies of occupational disease in genetically susceptible workers; (3) cross-sectional evaluations of the prevalence of disease among genetically differentiated groups; (4) case-control studies of the association of genetic characteristics and disease; and (5) family studies of disease aggregations. These approaches, in part, allow for controlling genetic factors or identifying susceptible genes or phenotype markers that may differentiate occupational populations according to risk. However, in many of the studies evaluated, the methods used were not very powerful for detecting gene-occupation interactions. More powerful designs need to be utilized for the simultaneous assessment of genetic and occupational risk.

Genetic factors rarely have been considered in studies of occupational health risks, for a variety of reasons. These range from the overwhelming effect of occupational exposures as compared to genetic influences for some diseases to concerns that emphasis on genes will be to the detriment of efforts to control the environment. In many of the classic occupational studies, the objectives were etiologic and the exposures were so substantial that exposure-disease relationships could not generally be measurably confounded by genetic factors. Despite the strong causal associations that have been detected in many occupational studies, there remains a differential distribution of diseases among workers that cannot be accounted for by differences in exposures, work practices, or life-style. Genetic factors are likely to be responsible for some of this distribution.[1] It is clearly accepted that practically no disease is determined solely by either genes or environment.[2,3] In the early history of occupational epidemiology, genetic influences were considered only in terms of controlling for confounding by race and sex. Today as many occupational exposures are being controlled to lower levels, the importance of genetic factors as sources of variability in risk estimates is increasing. This is not to imply that occupational etiologies will be replaced with genetic etiologies, rather, that genetic factors, which might confound exposure-disease associations, should be included as relevant variables in study design and analysis.

Newly developed techniques from molecular genetics and biochemistry offer a range of capabilities for research. For example, it is now possible to compare directly DNA sequences of case subjects and control subjects for genes potentially involved in disease etiology.[4,5] These types of techniques also enable identification of "susceptibility" genes or, at least, phenotypic expressions that may differentiate populations according to risks. Techniques also exist in epidemiology and genetic epidemiology for disentangling gene-environment interactions.[4]

Given these developments, it is time to review the status of research on the simultaneous study of genetic and occupational factors. Despite the increasing volume of occupational epidemiologic research, the portion involving gene-occupation contributions and interactions is minuscule. It has, therefore, been possible to review the majority of research on this topic, and analyze and characterize the nature and extent of it. The emphasis of this paper is on the methodologies used in research and the directions future research might take.

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The occupational health and pertinent medical research literature was searched for examples of studies involving both genetic and occupational factors. Use was made also of published reviews of this topic.[1,6-8] Because the simultaneous consideration of genetic and occupational factors is rare, this approach was likely to result in a representative survey of the field.

Five methodologic approaches were found to be used most frequently in the research reviewed: (1) adjustment for confounding by race, ethnicity, and sex; (2) case studies of occupational diseases in genetically susceptible workers; (3) cross-sectional studies of the prevalence of disease among genetically differentiated groups; (4) case-control studies of the association of genetic characteristics and disease; and (5) family studies of disease aggregations. The studies discussed have been selected for representativeness in design and analysis and not for the findings. The details presented for each study are discussed to the extent to which the general nature of the study can be understood and the methodology can be elucidated.

Adjustment for Confounding by Race, Ethnicity, and Sex

A common, but crude, method of considering the potential influence of genetic factors is the use of race-specific disease rates and strata in the computations of expected numbers of cases and in the stratification of results. Matching is also often performed in terms of race. The reason for race specificity is that many diseases differ markedly in frequency or severity, or both, by racial or ethnic group.[9,10] The differential risk of disease by racial group is manifest in two ways. First, there are certain innate racial characteristics (eg, skin color, lung volume, acetylation polymorphisms), expressed by all, or substantially all, members of a race that put that race at high or low risk to disease.[6,10,11] Second, some of the observed differences in disease distibutions and risks according to racial group are related primarily or solely to socioeconomic or cultural factors.[12] The extent of this confounding has been frequently debated. Additionally, in occupational studies, apparent racial or ethnic differences in observed disease rates may simply reflect job assignments and differential exposures rather than race-specific susceptibilities. For example, an excess of lung cancer among "nonwhite" workers in the coke plant of a steel mill was later attributed to the fact that "nonwhite" workers worked in or around the coke ovens which emit lung carcinogens, and the white workers generally did not.[13,14] If there was an additional genetic (racial) component, it was not assessed. In another study of a chemical plant, black workers who had higher rates of bladder cancer than white workers more often were given the job of standing in vats of β-naphthylamine and breaking up crystallized chunks of it.[15]

The use of racial or ethnic specificity to control for genetic susceptibility is only a crude approach which takes advantage of the fact that genetic traits aggregate along racial or ethnic lines. Although this approach is useful for comparability of study groups, it provides little information to clarify occupation-disease associations. Moreover, in addition to the fact that race is correlated with socioeconomic and cultural factors, race as a biologic or genetic tool of analysis is limited because it represents a false homogeneity of groups based on superficial characteristics such as skin color. In epidemiologic or genetic terms this is not particularly helpful, since there are many physiologic and health variations that occur among persons with the same skin color as well as among those of different colors.[16]

Adjustment for confounding by ethnicity, beyond that coincidental with race, is rare in occupational studies. This is because data on ethnicity is usually not gathered, sample sizes of such studies usually are too small for stratification, and ethnic differences are more likely to be environmental rather than genetic. Nonetheless, ethnicity can be an important factor in occupational studies since some diseases vary according to ethnicity,[9] and occupational groups within the same locality can vary with regard to ethnic composition.[17] Ethnic factors, genetic or environmental, may confound exposure-disease associations. This makes the selection of comparison groups more problematic.

Sex is also considered as a genetic trait. Various genetic traits and disease susceptibilities aggregate according to sex.[18-20] The most obvious examples are those that pertain to anatomic or physiologic features that are sex-specific. Less obvious are diseases such as diabetes mellitus that are common to men and women, but for which there are clear sex differentials and possibly susceptibilities.[20] However, behavioral and lifestyle factors may be responsible for some of the differential disease rates according to sex.[18,21] Adjustment for confounding by sex is similar in methodology to that for race.

Case Studies

Case studies of workers genetically susceptible to occupational disease have been reported.[22,23] Classic examples are the published reports of lead or benzene poisoning in workers found to have the β-thalassemia phenotype. Simson and Shandar[22] characterized three such cases in which workers had reduced hemoglobin and abnormal red cell morphology (poikilocytosis).

Saita and Moreo[23] reported three cases of chronic occupational benzol poisoning (anemia) in which diagnostic difficulties were overcome when it was discovered, through laboratory tests on patients and their relatives, that there was a pre-existing thalassemic trait.

Some of the weaknesses of case reports in providing definitive information on gene-occupation interactions can be seen in the issue involving pilots and other flight personnel who have sickle cell trait. Early case reports on incidents of sudden unexplained deaths in persons with the sickle cell trait have been reported.[24-26] Green et al[26] reported a case of a nurse who, in an airplane flying at 10,000 feet, developed acute abdominal pain

presumably from an infarctive incident in the small bowel. The authors inferred that, because later testing showed her to be a sickle-cell trait carrier, this was the predisposing condition.[26] However, subsequent criticisms in the literature pointed out that a normal hemoglobin level in association with a positive sickle cell trait screening test does not preclude the coexistence of some other abnormal hemoglobin that could contribute to altitude intolerance.[27] A review of a large series of case reports by McKenzie[28] concluded that sickle cell trait in the absence of a sickling crisis, unusual difficulties in anesthesia, or known contributing factors, is no basis for suspecting intolerance to moderate altitudes.

The case study approach is quite limited in assessing gene-occupation interactions, since it is not analytical. Case studies, however, may serve as reports of sentinel events, and thereby provide hypotheses for subsequent testing. Since many of the genetic factors that have occupational health significance are rare, case studies may remain an important source of information.

Cross-sectional Studies

The cross-sectional study by Chan-Yeung et al[29] demonstrates the quantitative evaluation of the relationship between a genetic factor and a health outcome in the presence of an occupational exposure. A group of 1,138 workers in dusty industries (saw mills and grain elevators) was evaluated to determine whether workers with partial deficiency in serum α_1-antitrypsin, as indicated by the PiMS and MZ phenotypes, had a greater prevalence of chest symptoms and lung function abnormalities than those with the most common phenotype, PiM. All workers were administered occupational health questionnaires and lung function tests. Blood specimens were collected for phenotyping. Interphenotypic differences for personal and employment characteristics were evaluated, and no differences were found in mean age and height, the proportion of workers exposed to different kinds of dusts, or the duration of exposure. There were, however, significant differences in smoking habits. The PiMZ phenotype workers included a very small percentage of nonsmokers (6.5%) but a larger percentage of ex-smokers compared with workers of other phenotypes. Thus the prevalence of chest symptoms and lung function abnormalities was analyzed in groups stratified by smoking habits. The prevalence of abnormalities among the three Pi phenotype groups was compared within each smoking stratum but no statistically or clinically significant differences were found. The association of pulmonary function and duration of employment was assessed for the three Pi phenotype groups by evaluating the linear relationship in a regression analysis. For those workers who had the M and MS phenotypes, a significant negative association was found between forced expiratory volume and the maximal expiratory flow and the duration of employment.[29]

Another example of the cross-sectional approach was demonstrated by Silverstone and Searle,[30] who attempted to determine whether genetic or environmental factors appeared to account for susceptibility to skin cancer. Occupation, characterized dichotomously as "indoor" or "outdoor" employment, was a main environmental factor. The genetic factors included ancestry, eye color, complexion, and skin reaction to the sun. Long-term residents of three widely separated regions of Australia were surveyed, and univariate and multivariate analyses were used to discriminate between cases of skin cancer and noncases on the basis of the variables of interest. The investigators concluded that the genetic factors were of greater importance than the environmental factors.

In another example, a cross-sectional study was performed to determine whether workers in four chemical industries were at increased risk of hemolytic anemia due to erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. This was considered likely, since certain therapeutic drugs have been shown to cause hemolytic anemia in patients with G-6-PD deficiency. Szeinberg et al[31] determined the prevalence of G-6-PD deficiency and hemolytic anemia in workers in four plants (munitions, pharmaceutical, tire, textile-dyeing) who manufactured or handled chemicals capable of causing hemolytic anemia. The worker population consisted of "Middle Eastern" workers, an ethnic group known to have a relatively high frequency of G-6-PD deficiency. Each worker was tested for G-6-PD deficiency and administered a questionnaire for medical and occupational history. Of 241 workers evaluated, 25 (10.4%) had G-6-PD deficiency, and none of the 25 had a history of hemolytic anemia. No environmental measurements were made, and the findings do not preclude that, under other working conditions, different results would be obtained.

These three examples[29–31] show attempts to identify genetic components in occupationally induced disease by determining the prevalence of the disease and the genetic characteristics. Cross-sectional studies have limited value for assessing gene-occupation interactions because the genetic component was usually restricted to a single individual rather than a family or pedigree. Although it is uncommon in cross-sectional studies to define genetic factors beyond their presence or absence in the individual, it is possible if a family history is taken. It also is possible in cross-sectional studies to calculate the role of genetic factors in differentiating cases and noncases, and to determine interaction between genetic and environmental factors and calculate the etiologic fraction for each of them.[32] Unlike most cross-sectional studies, those which identify genetic variables allow for some reflection on temporal aspects, since the genetic factor is likely to have preceded the exposure or disease outcome.

Case-control Studies

The most common method of assessing the role of genetic factors in occupational disease has been the case-control approach. Heise et al[33] used a matched case-control design to evaluate the role of HLA phenotypes in the development of coal workers' pneumoconiosis (CWP). Cases of progressive massive fibrosis were

matched with cases of simple CWP or individuals with no evidence of disease. Matching was done on age (in years) and duration (in years) of employment in mining. There were no significant differences in frequencies of HLA antigens between the progressive massive fibrosis group and the CWP group, so these were combined for comparison with the control group. The combined group differed from the control group with respect to the frequency of HLA-A1. The frequency of HLA-A1 among the combined pneumoconiosis groups (21.6%) was significantly less than among the control group (31.3%) ($P = .045$). The frequency of HLA-A1 among control groups was almost identical to that reported among the US population (32%)[34] However, when corrected for the number of antigens tested, the difference is not significant ($P = .089$). The risk ratio of CWP among miners with HLA-A1 relative to that among miners lacking HLA-A1 was 0.60.

The use of the HLA antigen system presents certain methodologic limitations which need to be considered. Often, several HLA antigens will be compared in the same study and these antigens are not independent. Antigens belonging to the same segregant series are negatively associated, and thus the increase of one antigen frequency leads to the decrease of another.[35] It is generally better to consider each series separately.

The HLA-disease associations currently known are characterized by increased frequencies of one or more of the antigens, whereas decreased frequencies are less pronounced and most likely secondary to those increased. When interpreting retrospective studies of lethal diseases, one must consider that positive HLA associations may indicate resistance to progression of the disease.[35,36]

Rystedt[37] used a case-control design to evaluate the role of the immunogenetic condition of atopy as a predisposing factor in the development of work-related hand eczema. A four-group design was used: 509 individuals with severe atopic dermatitis in childhood (group 1); 406 with moderate atopic dermatitis in childhood (group 2); 222 with respiratory allergy, but no atopic dermatitis (group 3); and 199 without personal or family atopy (group 4). Each group was administered a detailed medical and occupational history questionnaire. Occupational exposure was differentiated into three categories ranging from slight to excessive exposures to chemicals, water, soil, or wear. In groups 1, 2, and 4, there was a slightly significant difference between the frequency of hand eczema in individuals with and without occupational exposure to chemicals, water, soil, or wear. The frequency of hand eczema was markedly greater in individuals with a history of atopic dermatitis compared to those with non-atopic dermatitis.

Snodgrass et al[38] evaluated the enzyme aryl hydrocarbon hydroxylase (AHH), which had been previously shown to be one of the genetically determined pathways for the metabolism of polycyclic aromatic hydrocarbons, and hence potentially indicative of susceptibility to polycyclic aromatic hydrocarbon-induced lung cancer.[39,40] A variant of the case-control design was used. Four groups were compared for the level of induction of AHH. The four groups were: (1) noncancer patients without asbestos exposure, (2) noncancer patients with asbestos exposure, (3) lung cancer patients without asbestos exposure, and (4) lung cancer patients with asbestos exposure. Smoking histories (in pack years) and duration of asbestos exposure (in years) were determined by questionnaire. AHH was assessed in both pulmonary macrophages and blood lymphocytes. When the cancer and noncancer groups were compared, those individuals with asbestos exposure showed increased AHH activity. An exposure gradient in AHH activity was observed proceeding from group 1 to group 4, with the percent of each group with high AHH activity as 31%, 43%, 64%, and 100%, respectively. Although there may have been a genetic basis for the lung cancer response pattern due to differential antecedent AHH activity, it also appeared that AHH activity was induced by the exposure to asbestos. The study did not differentiate between these two phenomena.

A better example of a hereditary enzymatic polymorphism can be found in the study by Cartwright et al[41] which involved a case-control design to evaluate the role of the genetically determined polymorphism of the enzyme *N*-acetyltransferase in aromatic amine-induced bladder cancer. This enzyme is a predisposing host factor and has been shown to play a role in the detoxification of carcinogenic aromatic amines. The slow acetylator phenotype has been linked to malignant disease in animals exposed to aromatic amines.[42] In the case-control study, case and control subjects were classified by occupational history in the chemical (generally dye) industry and quantitative expression of the phenotype (as determined by administration of a tracer drug metabolized by the *N*-acetyltransferase pathway). The proportion of slow acetylator phenotypes was 96% in subjects who were chemical industry workers compared with 59% for those who had never worked in the chemical industry ($P < .0005$). Additionally, the slow acetylator status was associated with more high-grade carcinomas. This study is a paradigm for gene-occupation interactions for occupational cancer. The genetic component is the slow acetylator phenotype which is an autosomal recessive trait, measured on a continuous scale and defined as a set of values that correspond to the rate of acetylation.[43] Persons who are slow acetylators have about one ninth the acetylase activity of fast acetylators.[44] This phenotype is prevalent in 50% of North American white and black populations but differs in other ethnic and racial groups.[6] The environmental component is aromatic amine exposure. The result of the interaction is a higher risk in exposed persons with the slow acetylator phenotype compared with persons who either have no exposure or do not have the phenotype. Other endogenous or exogenous factors may influence this interaction; the basic paradigm is supportable.

Familial Aggregation Studies

Familial aggregation studies represent an approach classically used in genetic epidemiology to lay the foundation for discovering genetic factors important in gene-

environment interactions. With regard to occupational factors, most of these studies have been of the case-control design but, in some instances, the approach involved assessing risk factors in relatives of case and control subjects. For example, Ooi et al[45] adjusted for occupation in attempting to determine whether there was a familial risk for lung cancer. The analysis involved 336 subjects (probands) and 307 control subjects (probands' spouses). First-degree relatives of probands compared with first-degree relatives of controls showed a strong excess risk of lung cancer after controlling for occupational exposures, cigarette smoking, and other risk factors. Occupational exposures were accounted for by developing a cumulative index of exposure to occupation and industry. Scores were assigned to occupational exposures according to the degree of risk. Stepwise logistic regression was used to relate the probability of a lung cancer outcome among relatives to a set of predictors including occupation.[46] The authors believed that their findings might be interpreted to support the presence of a susceptibility gene to lung cancer. Previously, Joishy et al[47] suggested that a gene(s) determines the susceptibility of pulmonary cells to malignant transformations by oncogenic agents and affects the histologic features and metastatic behavior of resulting neoplasms.

In a more traditional approach, Kantor et al[48] performed a population-based case-control study to assess familial and environmental (including occupational) interactions in bladder cancer. Structured questionnaires were administered to 2,982 case subjects and 5,782 control subjects to determine family history of urinary tract cancer, individual occupational and medical histories, and the use of tobacco, artificial sweeteners, and coffee. Risks associated with familial history were highest among persons under age 45 (RR = 1.48), in women (RR = 1.8), in nonwhites (RR = 2.0), and in persons with French, German, and Scottish heritage (RR = 2.4, 1.8, 1.7, respectively). The overall risk associated with familial history is 1.45. A history of employment in high risk occupations was not significant (RR = 1.0).

Weiss et al[49] have criticized the incidental collection of family history data in the course of a case-control or similar study for the following reasons: (1) poor statistical properties of standard relative risk measures; (2) interpretational problems of observed relative risks when affected cases arise from genetic as well as nongenetic causes, and when genes may not always be expressed in individuals in whom they are present; and (3) confounding effects which may occur when a high-risk allele alters the age of onset pattern of the disease. These problems result largely from a loss of design control over the degree of exposure of individuals ascertained, and can lead to small observed relative risk even when genetic factors are significant.[49]

A study by Wrensch[50] illustrates a unique attempt to resolve genetic-occupational interactions. Wrensch evaluated the relationship between occupational and familial factors and brain tumors by using the same case group but two different control groups. One control group was used to test the association of occupational factors and the other to test the association of familial factors. Ascertainment of the familial occurrence of brain tumors, although not necessarily a genetic factor, would, if found, lay the foundation for discovering genetic factors.[50] Finding no familial association would indicate that genetic factors are unlikely to be important. The rationale for selecting two different sets of controls was related to the nature of the hypotheses tested. For the familial hypothesis, families of subjects' wives were compared to subjects' families. This minimized a common source of bias in case-control family history studies; namely, subjects' families are more likely to be aware of diseases of interest than families of unaffected control subjects. For the occupational hypothesis, a brother and/or brother-in-law or friend of each subject was selected as a control subject for each case. A maximum of 2 controls per case were selected. Case subjects were matched for age. The rationale for selecting these controls was that a comparison group was needed that was derived from the same population as the subjects, but, since the hypothesis included residential variables, neighborhood control subjects were ruled out. The frequencies of brain cancer in subjects' and wives' relatives did not differ; however, cancers of all sites were more frequent in subjects' than in wives' relatives.

The interpretation of familial aggregation of disease is complicated by the fact that it could be due to genetic or environmental factors, or merely a random distribution. The incidence of cancer and other diseases is usually high in some families, even after adjusting for environmental variables.[51] At the same time, a family is likely to have very similar environmental exposures. Familial occupational disease patterns in addition to genetic factors may be due to parents' having the same jobs as the children, or to secondary exposure of offspring from contaminated clothes or other items brought home by parents. Consequently, family studies need to consider both genetic and occupational explanations as well as some model of interactions.[4,51]

Noweir et al[52] used a cross-sectional design to evaluate the role of family susceptibility in the development of byssinosis among workers exposed to flax dust. Each of 475 workers was administered a medical and occupational questionnaire about himself, as well as the occupational history of his father, grandfather and sons who were involved in flax processing. A medical examination of the workers was also performed. The prevalence of byssinosis was significantly higher ($P < .05$) among workers whose fathers had no history of exposure to flax dust compared to those workers whose fathers did have such exposure. Age and smoking habits were controlled in the analysis. The authors concluded that the study showed family susceptibility, but that further research was needed to distinguish whether this was due to hereditary or immunologic factors.

Another cross-sectional study, of Egyptian workers exposed to silica dust, revealed an apparent genetic association. Silicosis risk was related to the degree of consanguinity of the workers' parents.[53] Noweir et al[53] found that the silicosis risks were highest in workers

whose parents were cousins to each other (degree not specified) compared with workers whose parents were more distantly related or not at all related. The study found that, when the parents were cousins to each other, the exposed sons had a greater prevalence of silicosis (52.9%) than did the exposed sons of parents who were either distant relatives (36.1%) or not related (40.0%). This had been demonstrated previously, since consanguineous marriages provide a chance for pathologically homozygous recessive characteristics to be expressed.[54] Workers with blood groups O or A had greater prevalence of silicosis than those with other blood types ($P < 0.05$).

Discussion

Conceptual Basis

The study of gene-occupation contributions and interactions has been relatively rare. Of approximately 2,000 genetic diseases identified in humans, only a few have been studied to assess whether, and to what extent, genetic conditions may predispose persons to environmentally induced disease.[55,56] Equally rare has been the effort to evaluate whether known occupationally induced diseases have a genetic component. Failure to seek these interactions is not the result of a lack of fundamental concepts.[7,57–61] Since 1917, researchers have speculated that genetically determined hypersusceptibility may predispose workers to occupational disease.[58] Since the 1950s the terms "pharmacogenetics,"[59] "ecogenetics,"[60] and "occupational ecogenetics"[61] have been used to express the fields of study of the interaction of genetic factors and exogenous agents. By 1975, a report by the National Academy of Sciences listed 92 human genetic disorders believed to predispose the affected individuals to the toxic effects of pollutants.[62] More recently, King et al[4] reviewed five established methodologic approaches for disentangling genetic and environmental influences on disease distribution: (1) twin studies, (2) adoption studies, (3) path analysis, (4) analysis of the cultural transmission of disease risk factors, and (5) studies of association between specific genotypes and diseases. The method of choice, however, depends on the disease and the study design.

In most of the studies reviewed in this manuscript, the methodologies for the assessment of the interaction of genetic and occupational risk factors were of limited effectiveness. One reason for this is that genetic and occupational factors usually do not act in a simple manner that can be expressed as two dichotomous independent variables. Although the most straightforward case studies involve simple Mendelian inheritance wherein a single gene is "highly penetrant," most cases have a major gene that is of low penetrance with most of the carriers not expressing the disease.[63] If studies in this area are to be informative, it is necessary to identify genetic markers for specifically inherited diseases and then identify the occupational and behavioral differences between gene carriers who do and do not express the disease. With occupational diseases the concern may not be for inherited disease but rather for an inherited polymorphism such as the slow acetylator phenotype that predisposes an individual to disease under certain conditions of exposure. It is important to determine whether these are to be treated as confounders or as independent variables.

Most occupational diseases may also involve the effects of several genes, rather than a single gene, and many environmental factors. It is necessary to refine further techniques for including and handling such multifactorial situations. Too often in occupational studies, genetic variables have been excluded from multivariate models for evaluating disease risk factors, because surveys have included nothing more than a broad question on family history.[64]

Types of Data

Different types of data are appropriate for evaluating specific components of the gene-occupation interaction.[64] The genetic component is best determined with data from pedigree studies; the occupational component is best determined from case-control and cohort studies. One solution to the dilemma is to map a gene and then study a cohort of individuals with the susceptible genotype and a set of nonsusceptible controls so that gene-occupation interactions can be clearly defined.[64] Using genetic markers from DNA cloning enables such gene mapping. In the past, gene products were the only tools available for the investigation of genes. Now, with DNA probes (cloned segments of DNA that will specifically hybridize to the gene or segment of DNA being studied)[65] available for analysis, it is possible to identify the underlying nature of genetic defects.[4,5] DNA probes such as restriction fragment length polymorphisms represent a recent dramatic breakthrough in gene marker strategies[5] in which variations in biochemical patterns of the DNA molecules themselves are examined.[5,63,64] One single biologic specimen (DNA material from the nuclei of leukocytes from about 20 ml of ordinary venous blood) has the potential of providing polymorphic genetic markers that can map major genes on virtually any chromosome in the body. Once these markers are generally available, known gene carriers can be studied for other factors to identify exactly which occupational, environmental, and life-style factors affect a given gene's expression.[63] In these instances, prospective and case-control studies will be useful.

Selection of Traits

It is worthwhile to consider what genetic traits might be useful in occupational epidemiologic studies. Obviously, a trait of interest would be one that modifies or confounds an exposure-disease relationship. It should be a trait that is frequent enough so that there could be efficient statistical analyses. Samples of sufficient size

are likely to be found for traits that involve relatively large groups of workers such as those exposed to polycyclic aromatic hydrocarbons (trait: metabolic oxidation phenotype or aryl hydrocarbon hydroxylase), to parathion-containing pesticides (paraoxonase phenotype), or to substances that induce emphysema (trait: serum α_1-antitrypsin).[29,38,66,67] In selecting a trait for inclusion in a study, it is important to hypothesize what the role of the genetic trait is in response to an occupational condition. Is the mechanism of gene action additive or nonadditive? Could there be epistasis? Is the trait being monitored the phenotypic or genotypic expression? Is there an increased risk for homozygous, heterozygous individuals, or both? Can the heterozygous individual be identified? What is the mode of inheritance? Even when these questions are considered, there is still a need to bring together in a study an appropriate model to define gene-occupation interaction and statistical methods which make it possible to extract meaningful inferences.

Particularly troublesome are traits that show continuous gradations of expression rather than discrete phenotypes. These require an approach based on the use of measurement rather than the frequency approach upon which Mendelian ratios are based.[68] Continuous traits do not allow for easy classification of individuals into distinct, unambiguous phenotypes. This has similar implications for epidemiologic research as do the problems of misclassification of exposure and outcome variables. Four main models of the mode of inheritance for traits expressed as continuous variables have been identified: (1) the major gene model—one or two loci and few alleles, (2) a polygenic model—variation in the trait results from a blend of many approximately additive genetic effects plus a myriad of environmental perturbations, (3) a mixed model—the combination of a major gene and polygenes, (4) a model of no genetic inheritance where variation is due to sporadic and/or complex environmental factors.[69]

Additionally, other host factors such as age, nutritional status, and pre-existing diseases that confound genetic-environmental interactions need to be identified and considered. For example, workers with G-6-PD deficiency may be at increased risk of hemolytic anemia from various chemical exposures, but it is also likely that their nutritional status may be able to mitigate or enhance their susceptibility.[70]

The interpretation of studies that identify genetic and occupational factors is not without pitfalls. What appear as genetic effects may be due to other host or environmental factors that have not been adequately considered. A degree of genetic diversity, possibly even differences in enzyme activity conferred by different alleles at a locus, may not result in differences in susceptibility. Different alleles may coexist because they do not differ in the susceptibility they confer.[6]

The status of the assessment of genetic factors in occupational disease studies appears to be in much the same place as was the assessment for cigarette smoking in occupational disease research about 20 years ago.[71] This is evidenced by the small number of studies available for this review and the relative analytical weakness of those studies to go beyond, essentially, general correlations. It is not likely that it will be necessary to wait 20 years until genetic factors are more frequently considered, because of the rapidly improving developments in genetic markers, particularly DNA polymorphisms,[5] the extensive methodologic approaches in genetic epidemiology,[4] and the continuing identification of susceptible phenotypes[7,55] available at this time. The benefits of clarifying the role of genetics in occupational disease are that there should be a clearer understanding of mechanisms of occurrence and further opportunities for prevention and control.

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