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Session IV. Applications of Biomarkers in Occupational Medicine

USE OF BIOLOGICAL MARKERS IN OCCUPATIONAL HEALTH RESEARCH AND PRACTICE

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The promise of biological markers in occupational health research and practice has been described in the scientific literature. The current generation of biological markers has the potential to allow for the earlier detection of disease, for the reduction of misclassification of exposure and outcome, for heightened understanding of mechanisms and etiologic pathways, and for the designation of groups at risk. What is necessary now is a strategy for realizing this potential. The elements of such as a strategy may include the following: (1) a program to validate biomarkers, (2) increased utilization of valid biomarkers in etiologic and prevention research, and (3) developmental programs to encourage interdisciplinary collaboration and train molecular epidemiologists. A framework for linking biomarkers and epidemiologic study designs has evolved during the part 5 yr. For this progress to continue, it is important that discussion about biomarkers reflect a specificity with regard to both the type of marker and the use for which it is intended.

There is a rapidly growing literature that describes how biological markers can be used in occupational and environmental health research and practice (Perera and Weinstein, 1982; Lauwerys, 1983; Grieco, 1987; NRC, 1987; Cullen, 1989; Schulte, 1991). This literature is built on a broad foundation that includes almost 30 yr of biological monitoring experience in occupational health and the more recent explosion of information from molecular biology, analytical chemistry, and toxicology, culminating in the past 5 yr with examples of the use of biological markers to better indicate exposure, outcome, and susceptibility (Brandt-Rauf, 1988; Henderson et al., 1989; Ashford et al., 1990; Vineis, 1992; Schulte et al., 1992). These were linked in a continuum described by the NRC (1987).

For the most part, those first descriptions were by the laboratory scientists. More recently, epidemiologists have attempted to "flesh out" the epidemiologic portions of the term molecular epidemiology, which has come to characterize this approach (Hulka and Wilcosky, 1988; Schulte, 1987, 1989; Vineis, 1992; Schulte and Perera, 1993).

Previous efforts using biomarkers—that is, previous molecular epidemi-

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ologic research—have not shown attention to epidemiological principles involved in subject selection, sample size determination, control of confounding, interpretation and communication of results, impact of results, and follow-up. In part, this was justified since these were laboratory studies designed to develop a marker or an assay. However, for use in populations, there are further developmental efforts required. These pertain to understanding how the marker varies by demographic and behavioral factors, the prevalence in populations, the predictive value of the marker, and questions on interpretation and follow-up. To this end, I would like to address three efforts that could enhance current efforts to utilize biomarkers in occupational and environmental health research and practice.

DEVELOPMENT OF A PROGRAM TO VALIDATE BIOLOGICAL MARKERS

As a first step, a biomarker needs to be shown to be valid. There are three types of validity research that coincide with the three types of biomarkers: exposure, effect, and susceptibility (NRC, 1987).

Validate the Relationship Between Exposure and Dose

Exposure	→	Internal dose	→	Biologically effective dose

Markers of exposure may be validated by assessing the relationship of an exogenous exposure and internal dose or biologically effective dose. Critical in such research is the need to have an effective exposure assessment. This may require a combination of personal and environmental monitoring and questionnaires, record review, and modeling to reconstruct exposure history. The approach also requires understanding of the pharmacokinetics involved for the particular xenobiotics. Related to this is the need to understand the natural history of the marker and utilize it in the validation study. For example, in a study of hydroxyethyl hemoglobin adducts in workers exposed to ethylene oxide, we used the life span of the erythrocyte (approximately 4 mo) as the time span in which to reconstruct exposure. There is also a need to account for factors that might influence the appearance of a marker. In the aforementioned study, an exposure response relationship was found, at levels below the permissible exposure level, when mean values were adjusted for important covariates such as age, cigarette smoking, and education (Schulte et al., 1992).

Validate the Relationship Between Biological Effects and Disease

Early biologic effects	→	Altered structure/ function	→	Disease

The lack of validation information in this category often bears much of the criticism about using biological markers. The often repeated question is, "What do they mean concerning health and disease?" These types of validation studies are difficult to accomplish because of the temporal factor. To identify an early effect—that is, an effect in pathogenesis or an effect predictive of disease—generally requires a prospective study design, although cross-sectional clinical studies of diseased and heavily exposed individuals can be used to great advantage. However, when not using a prospective design, care must be taken to avoid biased associations. This is often difficult, and hence, prospective studies are the best approach for validation. Prospective studies are expensive and time-consuming, and few are conducted. For example, despite the large number of studies on cytogenetic markers, there still is little consensus on their predictive value, since most of the studies have been cross-sectional and suffer from temporal ambiguity. Specifically, in epidemiologic terms, predictive value means the percent of those who test positive for a marker who actually develop the disease. To perform the appropriate prospective studies of sister chromatid exchanges would take a large population and a relatively long time. The best and possibly only example of such a study is the Nordic prospective study on the relationship between peripheral lymphocyte chromosome damage and cancer morbidity in occupational groups (Brøgger et al., 1990). Ten laboratories in four Nordic countries participated in a study of a combined cohort of persons (mostly from occupational groups) who had been cytogenetically tested. The cohort will be followed prospectively for cancer morbidity. The cohort is comprised of 3190 subjects, of whom 1986 subjects (62%) have been scored for chromosome aberrations and 2024 subjects (63%) scored for sister chromatid exchanges.

Validate Markers of Susceptibility

Exposure → Susceptibility → Disease

The tools of molecular biology and analytical chemistry have allowed researchers to identify a degree of interindividual variability not previously imagined (Janetos, 1988). Validated biological markers of susceptibility can serve as effect modifiers in epidemiologic studies. Effect modification is a term with statistical and biological aspects. Statistically, the examination of joint effects of two or more factors is often discussed in the context of effect modification. It depends on the statistical method (e.g., multiplicative or additive) used to model interaction. From the biological perspective, effect modification answers the question of why two similarly exposed individuals do not develop a disease. The answer, in part, is individual variability in metabolic and detoxification capabilities.

To validate a susceptibility marker it is important to minimize misclassi-

fication, which can occur by laboratory or epidemiologic factors that affect phenotyping or genotyping (Rothman et al., 1993). Next, it is necessary to demonstrate that the marker either increases the biologically effective dose or elevates the risk of disease.

The issue of the acetylation phenotype and bladder cancer in aromatic amines illustrates the susceptibility question (Vineis, 1992). Despite a plethora of studies, the scientific literature is still not conclusive on the extent to which being a slow acetylator modifies one's risk of bladder cancer. Generally, most studies have been too small, had weak exposure characterization, and were improperly designed to determine whether exposure or susceptibility was the key factor.

In what may be viewed as a classic study, Vineis (1992) and colleagues showed an example of how partial validation of a susceptibility marker might occur without using disease as the outcome. Vineis (1992) compared the formation of hemoglobin adducts (which are documented surrogates for DNA adducts which are believed to be involved in carcinogenesis) between individuals exposed to 4-aminobiphenyl and who were slow or fast acetylators. They found that the slow acetylators had an average of 1.5-fold greater frequency of adducts than the fast acetylators. Despite these encouraging efforts at validation, few markers of susceptibility have been validated, and none are ready for use in population screening (Schulte and Halperin, 1987; OTA, 1990).

Before biomarkers can be used for prevention and control of occupational disease, they need to be validated in the laboratory and in the population. This also means that methods for use in large-scale populations need to be developed. Currently, there is little research support for scaling up efforts needed for population studies. The types of validation and scaling efforts discussed here need close collaboration between laboratory scientists and population scientists (clinicians, epidemiologists, industrial hygienists, and exposure assessors). This is discussed in the next section.

The potential to identify susceptibility markers also presents policy dilemmas. Hornig (1988) has concluded, "The central policy question is: should variation in sensitivity of groups and individuals be taken into account in occupational laws and regulations?" This topic has many controversial aspects that revolve around issues of whether to focus intervention and control efforts on the individual or the environment. The heirarchy of controls used in occupational health involves focusing primarily on the environment (Schulte and Halperin, 1987).

INCREASED UTILIZATION OF BIOMARKERS IN ETIOLOGIC AND PREVENTION RESEARCH

Biological markers are tools that can be used in epidemiologic research. As such, they can supplement the already tried and true tools such as questionnaires, record reviews, exposure reconstruction and monitoring, model-

ing, and statistical analysis. The lesson learned from the early history of biomarker research is that biomarkers are tools that need to be used in conjunction with other data-gathering measures such as questionnaires, because there is need to account for the range of factors that can influence the appearance and frequency of biomarkers (Hayes, 1992). Nonetheless, with this perspective, validated biological markers may serve to reduce misclassification of independent of dependent variables, to allow for more homogenous case definitions, for detection of smaller amounts of xenobiotics, and for early biologic changes indicating disease risk.

A good example of how such markers can be used is the research by Groopman and colleagues that was able to discern the roles of aflatoxin B_1 and hepatitis B exposure in liver cancer (Groopman et al., 1985, 1992; Ross et al., 1992). Although an association between aflatoxin B_1 and hepatitis B exposure for risk of liver cancer has been demonstrated in several ecologic and questionnaire-based epidemiologic investigations, there has been continuing uncertainty regarding the precise role of aflatoxin in this relationship. In a series of studies, Groopman and colleagues first developed analytical methods to assess aflatoxin—DNA adducts in urine, then used the markers to detect lower cancer risk prospectively in a large cohort.

DEVELOPMENT OF PROGRAMS TO ENCOURAGE INTERDISCIPLINARY COLLABORATION AND TRAIN MOLECULAR EPIDEMIOLOGISTS

The validation and utilization of biological markers of necessity requires interdisciplinary collaboration. Such collaboration is not new to the field of occupational health—in fact, it has been the hallmark! It is not foreign to see an industrial hygienist, an analytical chemist, or other laboratory scientist as part of an occupational health research team. Still, there are different paradigms, languages, and assumptions between laboratory and field scientists that need to be addressed if there is to be effective collaboration.

There are also administrative barriers that must be overcome. These include issues of project direction. Who directs the project—the one who has the assay, or the one who has access to the population? There are also issues of source of funding. Laboratory-based study sections and funding sources are often disinclined to award funds for scaling up assays for population use, whereas epidemiologic- or clincial-based study sections or funding sources do not want to fund these efforts, which they view as basic research. A notable exception is the recent Request for Applications by the National Cancer Institute and the National Institute for Environmental Health Sciences, which invited investigator-initiated grant applications to further the effective use of biomarkers of exposure or susceptibility in future cancer etiological studies (NCI/NIEHS, 1992). There is a need for both the laboratory and the population scientists to appreciate what the other has to offer and to work in concert.

To foster collaboration it is useful to have a framework in which to consider and discuss with some specificity the type of marker and the use for which it is intended (Fig. 1). It is possible to consider biomarkers in terms of a continuum of events between exogenous exposure and resultant disease as one axis of a matrix and the type of study involving the marker as another axis (Schulte and Rothman, 1992). Four study types maybe considered: laboratory, where markers are developed; transitional, where markers are characterized for their use in population studies; etiologic, which are case-control, cohort, and prevention trials; and applied studies such as screening studies. The resultant matrix of biomarkers and study types can provide researchers, program managers, and decision makers with a frame of reference for discussing projects and describing collaborations.

Finally, the question arises of whether to train molecular epidemiologists de novo or to take laboratory and population scientists and supplement their training. Generally, we do not have a specialty program to train "questionnaire" epidemiologists or "PCR"-ologists; we do have programs to teach epidemiologists how to develop and use questionnaires and molecular biologists how to use PCR (polymerase chain reaction). Thus, in that regard, there is no rationale to train de novo molecular epidemiologists. On the other hand, use of biomarkers in epidemiologic research illuminates the epidemiologic paradigm of agent-host-vector, so that in addition to focusing on the effects of environment there is also need to focus on heredity, when using tools that reflect changes at cellular and molecular levels. If this is the case, and I think it is, then epidemiology training needs to be more biologically based. There have been a number of efforts among epidemiologists to reorient the field in this regard. This is not meant to downplay the importance of understanding social, cultural, behavioral, and political determinants of occupational and environmental disease. Rather, it is meant to

	Exposure	Internal Dose	Biologically Effective Dose	Early Biologic Effect	Altered Structure/Function	Clinical Disease	Susceptibility
Laboratory							
Transitional							
Etiologic							
Case-control							
Cohort							
Prevention Trial							
Applied							

FIGURE 1. Matrix of biomarker combinations and study designs. From Schulte and Rothman (1992).

encourage understanding of the biologic determinants that influence biomarkers.

There is also supplemental training that might be valuable from the laboratory perspective. This includes supplemental training in design and conduct of field studies that might be useful and serve to foster dialogue with population scientists.

Finally, in all efforts to validate and use biological markers in occupational and environmental health research and practice, there is need to consider the issues invovled in the interpretation and communication of results of marker tests. Use of markers has ethical and social implications. These issues should be addressed in study protocols prior to performance of validation, etiologic, or intervention research (Schulte, 1987; Omenn, 1982; Schulte and Singal, 1990; Ashford et al., 1990). Occupational and environmental diseases, like all diseases, are now being assessed at the cellular and molecular levels. Biomarkers as tools will be available whether we choose to use them or not. The challenge is to validate them and to use them effectively.

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