Biomarkers in epidemiology

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Biomarkers in Epidemiology

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A biomarker is a measurable event occurring in a biological system, such as the human body. In environmental epidemiology, a biomarker represents a subclinical and reversible change; it is not a diagnostic test, but an indicator that an early change has occurred that could later lead to clinical disease. Although some biomarkers may belong to more than one class, they are often separated into biomarkers of exposure, biomarkers of effect, and biomarkers of suceptibility. Biomarkers can be used to classify and quantify environmental exposures and their related effects, and many methods may be applicable in toxicological experiments as well as in epidemiology. Accordingly, biomarker epidemiology is undergoing rapid development and expansion and is becoming one of the most promising areas of environmental research. Although expanded applications should be encouraged, many biomarkers are poorly characterized, and attention should be paid to defining their properties in detail.

Indexing Terms: *environmental toxicology/epidemiology*

The term biomarker has entered the epidemiological and environmental vocabulary as a short form for biological marker or biochemical marker. The first European conference on biomarkers in environmental toxicology was held in 1993 (*1*). Biomarker refers to a measurable event occurring in a biological system, such as the human body (*2, 3*). This event is then interpreted as a reflection of a more general state of the organism or the life expectancy of an individual. In addition to biological marker (*2, 4*), other terms have occasionally been used with the same meaning. For example, a recent publication entitled "Biomarkers in ecotoxicology" (*5*) was referred to as "Bioindicators in ecotoxicology" in the table of contents. For the sake of uniformity, biomarker would seem to be the most appropriate term.

To be useful in epidemiology, the measurable event in the human body should represent a subclinical change only. A biomarker is not a diagnostic test, but an indicator that an early change has occurred that could later lead to clinical disease. Especially for use in preventive medicine, the change should be completely reversible. To trigger appropriate action, a biomarker finding should also be amenable to interpretation with regard to causal factors in the environment, and potential preventive efforts should be realizable, at least in principle. Also, from an ethical viewpoint (*6*), the practical use of the biomarker should be regarded as acceptable.

A biomarker reflects an event or a sequence of events that occur somewhere in the causal chain between an exposure to a hazardous factor and a related adverse effect. Theoretically, these events can be separated into those indicating "internal dose," "effective dose," etc., but some of these terms themselves are difficult to define, and a detailed classification of biomarkers may not necessarily add to the understanding of their properties. Nonetheless, three specific types of biomarkers are usually identified (Fig. 1) (*2, 3*). Although some biomarkers may belong to more than one class, they are often separated into biomarkers of exposure, biomarkers of effect, and biomarkers of suceptibility. As illustrated by papers presented at the Biomarker Conference in 1993 (*1*) and the present proceedings, all three types of biomarkers are extremely useful in epidemiological studies.

Exposure Biomarkers

An exposure biomarker may be a xenobiotic compound or metabolite within the body, an interactive product between the compound (or metabolite) and an endogenous component, or another event related to the exposure (*2, 3*). Most commonly, biomarkers of exposures to stable compounds are assessed by measuring their concentrations in appropriate samples, such as blood, serum, or urine. The concentration of a volatile chemical may be assessed in exhaled breath. If the compound is metabolized in the body, one or more metabolites may be determined, e.g., in a urine sample. Especially with mutagenic chemicals, some promising analytical developments have been realized (*7*). Adducts formed with DNA can now be detected in white

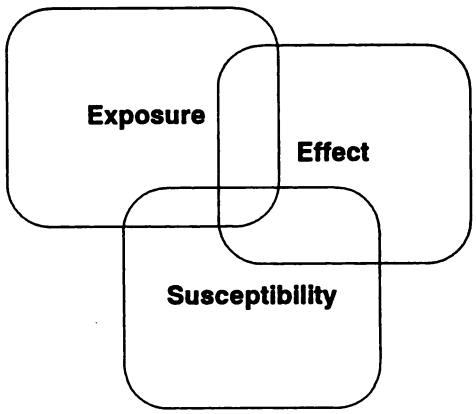

Fig. 1. Three major types of biomarkers have been recognized, but overlapping may occur.

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blood cells or tissue biopsies, and specific DNA fragments may be identified in the urine. Hemoglobin adducts may be a feasible biomarker, but no repair occurs, and they may not accurately reflect the effects in the target organ. On the other hand, hemoglobin adducts indicate the integrated event during the 4-month lifetime of red blood cells. One may speculate that adducts with other proteins, such as collagen, could become useful as indicators of exposures during much longer exposure periods. Although such adducts are the result of a biological effect, they are usually considered exposure biomarkers.

Temporal aspects are important for all exposure biomarkers, not only for adducts. Evidence must be obtained to show the extent to which short-term variations in the exposure affect distribution, retention, and interaction with the target molecules. Sometimes, such toxicokinetic evidence is used to classify a biomarker as an indicator of (total) absorbed dose or an indicator of effective dose (i.e., the amount that has reached the target tissue). Although few biomarkers have been fully characterized in this regard, extended application in epidemiology should be encouraged to assist in the elucidation of these aspects.

Effect Biomarkers

A marker of effect may be an endogenous component, or a measure of the functional capacity, or some other indicator of the state or balance of the body or organ system, as affected by the exposure. Such effect markers are generally preclinical indicators of abnormalities. These biomarkers may be specific or nonspecific. The specific biomarkers are useful because they indicate a biological effect of a particular exposure, thus providing evidence that can potentially be used for preventive purposes. The nonspecific biomarkers do not point to an individual cause of the effect; rather, they indicate the total, integrated effect that could be due to a mixed exposure.

As discussed, e.g., by Harris et al. (*7*), biomarkers may be crucial for the evaluation of genotoxic effects of environmental chemicals. In particular, methods used for assessing genotoxicity in humans may also be applied in animal experiments in which they can be compared with data on target tissues that cannot be examined in human subjects. Such studies of causal chains may provide new insight into disease pathogenesis. In this way, biomarkers constitute a common ground to be explored jointly by toxicologists and epidemiologists. Not surprisingly, this research area has attracted much attention, although predominantly in relation to cancer.

A recent publication from the International Program on Chemical Safety (IPCS) (*8*) reviews the applications of biomarkers, including those that indicate effects on different organ systems. Although very useful in this regard, it includes the following adverse health effects as examples of biomarkers: liver cell necrosis, decreased pulmonary function, low birth weight, and mental retardation. Thus, according to IPCS, certain medical diagnoses could be used as biomarkers. However, this application of the term may lead to confusion. The medical diagnoses mentioned should instead be referred to as sentinel events (*9*). A biomarker in the stricter sense of the word does not represent the diagnosis or the sentinel event itself, but rather reflects a risk that such pathology could develop at a later stage.

A biomarker therefore is like a symbol, which has a depth of meaning (regarding risk) greater than that represented by its immediate appearance (the change per se). Epidemiological evidence is of key importance to document the interpretation of the biomarker with regard to such risk.

Susceptibility Biomarkers

A marker of susceptibility, whether inherited or induced, is an indicator that the individual is particularly sensitive to the effect of a xenobiotic or to the effects of a group of such compounds. Most attention has focused on heterogeneities of enzymes involved in the metabolism of xenobiotics (*7*), although other nongenetic factors are likely to be at least as important. Hypersusceptibility is a well-known but insufficiently explored phenomenon in epidemiology. It may be due to an inherited trait, to the constitution of the individual, or to environmental factors (*10*).

A particularly promising aspect relates to hypersusceptibility caused by depletion of the reserve capacity. The human body seems to possess a certain capacity to withstand potentially adverse effects of chemical exposures. However, an individual's resistance toward chemical toxicity may be decreased by a preexisting disease or by additional environmental exposures, including those associated with diet and life-style (*10*). A previous exposure may not necessarily have resulted in recognized toxicity, but could conceivably have caused a weakening of body defenses, i.e., a decrease in the reserve capacity. Biomarkers of reserve capacity could therefore reflect both effect and susceptibility, e.g., related to the immune system, the hemopoietic system, or the kidneys. Such biomarkers would be particularly promising for epidemiological studies.

Applications in Epidemiology

As indicated above, biomarkers have important applications in epidemiology as well as in preventive medicine and environmental health. A major aim of epidemiological studies is to identify and evaluate risk factors associated with disease. Because of insufficient consideration of pathogenesis, risk-factor epidemiology has sometimes been referred to as black-box epidemiology (*11*). Biomarkers therefore fill a substantial need in modern epidemiology (Fig. 2). Hulka and Wilcosky (*4*) outlined the following purposes of using various biomarkers: (*a*) elucidation of pathogenic mechanisms; (*b*) improvement of etiologic classification of environmentally related diseases; and (*c*) recognition of early effects. In addition, some exposure biomarkers can be applied in groups of exposed workers to assess the

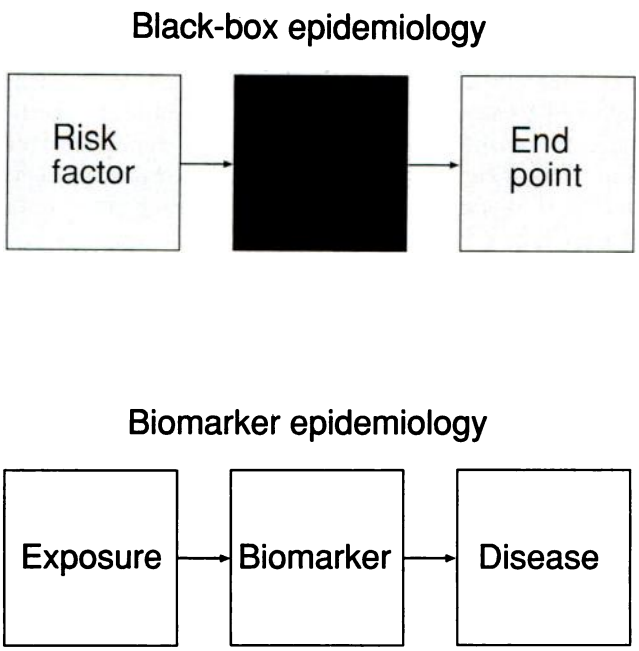

Fig. 2. The "black box" often apparent in risk-factor epidemiology may be effectively explored by the use of biomarkers as indicators of pathogenetic steps.

extent of compliance with pollution abatement regulations or effectiveness of preventive efforts in general. Biomarkers can also be applied to document the community impact of an environmental hazard. In healthy subjects, a biomarker may reflect individual hypersusceptibility to specific chemical exposures and may therefore serve as a basis for risk prediction. On an individual basis, a biomarker may be used to support or refute a diagnosis of a particular type of poisoning or other chemically induced adverse effect. These applications clearly relate to central issues in environmental epidemiology.

Conventional epidemiology has low sensitivity when exposure is assessed indirectly, or when assessment of the effects is based on crude indicators, such as diagnoses from death certificates. Because of the poor precision, misclassification is likely to occur, thus decreasing the sensitivity. Also, since major diseases take years to develop, conventional epidemiology concerns exposures of the past and may relate only partly to the problems of exposures today. In addition, environmental health research has to confront the thorny question of extrapolation from studies in experimental toxicology. Biomarkers represent an important instrument to tackle these problems.

Because biomarkers can be used in epidemiological studies to classify and quantify environmental exposures and related effects by methods that may even be applicable in toxicological experiments, biomarker epidemiology is currently undergoing rapid development and expansion and is becoming one of the most promising areas of environmental research. Again, some confusion has clouded the literature. Thus, papers on genotoxicity biomarkers first used the term "mutation epidemiology" (*12*), and subsequent publications usually referred to this area as "molecular epidemiology" (*7*). The molecules referred to were generally markers of genotoxic effects. Because genotoxicity could also be reflected by changes in morphology (e.g., aneuploidy), and because molecular biology methods may also be applied for other types of biomarkers, a more appropriate term for this field of research is obviously biomarker epidemiology.

Research Needs

Recent research has demonstrated the complexity of some dose–response relations and the considerable difficulty in identifying no-effect concentrations. For example, for most organic compounds, quantitative associations between exposures and the corresponding adverse health effects are not yet available; in many cases, even the primary target organs are not known for sure. Biomarkers are likely to be of crucial value in characterizing doses and effects in such studies. Extrapolation from animal experiments is becoming a sophisticated specialty within toxicology, and determination of comparable biomarkers in different species may provide important evidence in this regard. However, evaluation of toxicity data and biomarker results is often complicated by exposure to mixtures of substances, rather than exposure to a single compound at a time.

As already indicated by the proceedings (*1*) of the first Biomarker Conference in this series, multidisciplinary research is burgeoning and is likely to affect in a profound way both environmental epidemiology and toxicology, as well as preventive medicine. However, biomarkers, new and old, must be evaluated carefully with regard to their analytical, diagnostic, and etiologic validity. Toxicokinetic aspects, effects of other factors, and standardization of methodology must also be considered. These aspects have been clarified for only a handful of biomarkers so far, and the need to obtain such basic information is pressing. Schulte (*13*) recently asserted that "application of these markers has been less than optimum because of the failure of investigators to be precise about the type of marker that is needed or the specific purpose for which it is used." This criticism is somewhat harsh, but it does reflect the fact that in the beginning of a new research era insufficient attention is sometimes paid to characterizing the study variables. Given the growth in biomarker research of high quality and relevance, future research will hopefully remedy this problem.

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