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RESEARCH ARTICLES

Contribution of Biological Markers to Occupational Health

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Occupational diseases are now being assessed at the cellular and molecular levels; this presents new opportunities for prevention and control [Calleman et al., 1978; Ong et al., 1987; Stejskal et al., 1989; Welch and Cullen, 1988; Garry et al., 1989]. The key to these opportunities is the ability to detect biological markers that reflect exposure, response, and susceptibility. Biological markers are not new, however. Biological markers such as blood lead, urinary phenol levels in benzene exposure, and liver function assays have long been used in occupational and public health research and practice. What distinguishes the current generation of markers from previous markers is a greater degree of analytical sensitivity and the ability to describe events that occur earlier in the progression between exposure and clinical disease. There are now new domains of response that were not known to exist 20 years ago. Accompanying this sensitivity is the increased requirement to consider the numerous factors that can influence the appearance of biological markers. It has been observed that all workers with similar exposures do not develop disease or markers indicative of exposure or disease. Various acquired and hereditary host factors are responsible for this variation in responses. The role of assessing the nature and degree of variation between individuals is of paramount importance. Finally, the use of biological markers in occupational health research and practice also brings new ethical and legal considerations into high profile. This paper presents my personal opinions on how biological markers can contribute to occupational health efforts and the new requirements that they bring to the field. As with any technological change, the more we can anticipate the impact, the better our ability to adjust.

Key words: biological monitoring, disease markers, internal dose, occupational exposures

INCREASED SENSITIVITY

The current generation of biological markers has the potential to indicate minute interactions of xenobiotics and critical macromolecules and identify changes that occur earlier in the natural history of occupational disease. This ability to detect small quantities is illustrated by the change in units that are frequent measures of exposure

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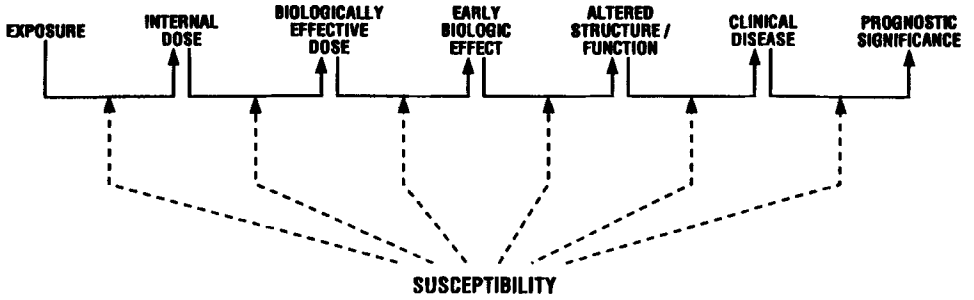

Fig. 1. Biologic marker components in sequential progression between exposure and disease.

or dose. For example, in 1970, when the Occupational Safety and Health Act (OSHAct) was promulgated in the United States, exposures generally were measured in terms of parts per million—units of the order of 10^{-6}. Now it is common to see papers with measures of dose (DNA adducts) in picomoles and femtomoles, units of the order of 10^{-12} or 10^{-15} [Calleman et al., 1978; Perera et al., 1988; Perera, 1987]. This is a billion times increase in sensitivity. The caution that has continually accompanied such technological change still holds today; our ability to measure outstrips our ability to interpret what is measured. Moreover, as our microview of xenobiotic exposures and subsequent effects unfolds, we begin to be confronted by an increasing number of vexing issues. For example, since we now have the capability to detect trace amounts of occupational toxins, other confounding substances found in trace amounts become important to consider in comparisons between groups of workers. Since biological markers essentially integrate over all routes of exposure, confounding factors need to be considered much more in measures of internal dose than in measures of airborne exposure. For example, unexposed workers who do not handle ethylene oxide have small amounts of hydroxyethyl adducts to hemoglobin [Van Sittert et al., 1984] that are found in higher concentrations in exposed workers. The source of those adducts may be cigarette smoke, some other environmental influences, or normal metabolic products. Thus, in the comparison of ethylene oxide—both exposed workers and unexposed workers—cannot start with a zero baseline. Another aspect of sensitivity is the potential ability to identify a heuristic continuum (Fig. 1) between exposure and disease and to characterize the steps in that continuum. This has been illustrated by the National Academy of Sciences (NAS) in the United States [National Research Council, 1987] and elaborated by others [Schulte, 1989; Hulka and Wilcosky, 1988; Hatch and Stein, 1987; Lauwerys, 1983]. According to the National Research Council (NRC):

> It is useful to classify biologic markers into three types—exposure, effect and susceptibility—and to describe the events particular to each type. A biologic marker of exposure is an exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. A biologic marker of effect is a measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease. A biologic marker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance.

With valid markers, it now appears possible that it is not necessary to wait for disease to occur before evaluating an association between an exposure and a disease in a group of workers. If, for example, a preclinical change predictive of disease is identified, then the same clinical and epidemiologic methods used in traditional epidemiology can be used to determine an association. This is illustrated in the paper by Hemstreet et al., [1988] in which DNA hyperploidy was shown to correlate with disease risk in workers exposed to 2-naphthylamine. Eventually, it should be possible to use effect markers (dependent variables) which appear very early in the exposure–disease continuum, that is, closer to the time of exposure. Similarly, exposure characterization no longer needs to be an ecological assessment, that is, the lumping of subgroups of workers into a single or a few categories of presumed exposure [Hulka and Wilcosky, 1988]. It is increasingly possible to distinguish workers by evaluating the dose to target tissues: these are the true "exposures" that result when workers with different work practices, physiological and metabolic characteristics, exposures, and so forth, are to be included in a study. Hence, from the exposure end of the continuum, it is possible to move forward in time toward the disease end. The classic epidemiologic paradigm of dichotomous exposure and disease classification (exposed or not, diseased or not) worked well in the past when exposures were large and effects detectable by alert clinicians and epidemiologists. Those days are gone in many countries. Today, exposures are generally less intense and effects subtler in many workplaces. In developing countries and in small businesses in developed countries, large exposures still occur. Courts and regulatory agencies are increasingly inclined to want evidence that accounts for the magnitude of occupational risks in light of other intervening factors. Current methods of clinical and epidemiological research can provide this evidence best when supplemented by techniques to measure biological markers of exposure, effect, and susceptibility.

OPPORTUNITIES FOR PREVENTION: PROMISE AND LIMITATIONS

The heightened sensitivity provided by emerging techniques for analyzing biological specimens presents great promise for prevention of occupational disease. The basis for this promise is that exposures and effects can be detected earlier in the continuum between exposure and disease, at a time before damage has occurred, and when the responses are fundamentally reversible homeostatic adaptations. The opportunity for control is then enhanced. We no longer have to be restricted to studying the mortality of an unfortunate cohort of workers so that future workers will benefit. The use of biological markers holds the promise that current workers also will be able to benefit, because environmental controls can be evaluated without waiting for disease to occur in order to indicate whether or not the controls are effective in preventing disease. Hence, biological markers constitute an early warning system to identify hazards or qualitative risk [Perera, 1987]. We no longer have to "count the bodies"; instead, we can count the molecules. The hope is that if environmental controls are put in place, measures of internal dose can give a true picture of whether or not the controls work. If a substance is suspected of causing cancer, genotoxic changes can be identified well in advance of reports of workers presenting with disseminated tumors. If subsets of the population are more sensitive and need more protection, they can be identified. Cullen [1989] has suggested that the use of biological markers in research center-based clinical investigations can provide great

opportunities for etiological and mechanistic research including: marker identification; exploration of surrogate markers; establishment of linkage between apparent early effect markers and late health effects; and the evaluation of "operational characteristics" of new markers. This approach cells for a biologically intense clinical examination of small groups of workers. For example, Welch and Cullen [1988] described bone marrow examinations in selected subcohorts of a population previously demonstrated to have hematologic abnormalities associated with exposure to ethylene glycol. By simultaneously measuring several peripherally measured indices, they determined a close correlation between myeloid hypoplasia in the marrow and certain red cell enzymes in peripheral blood. These findings pave the way for a sensitive early marker of effect for use in future field studies.

From the societal perspective of prevention of occupational disease, the hope is that biological markers can enhance quantitative risk assessment applicable to humans. This enhancement involves the ability to extrapolate from high to low doses and from laboratory animals to humans. Markers also can be used to quantify interindividual variability in susceptibility. These capabilities have generally been considered with regard to carcinogenesis, but they may be used in the assessment of most diseases [Hattis, 1987]. However, as this investigator cautions, the existence of new kinds of data that could be helpful in risk assessment does not in itself guarantee that they would be used, much less used effectively and appropriately in actual risk assessments. For this to be a reality, it will depend, among other things, on bridging the gap in understanding and techniques between the mathematically inclined scientists (epidemiologists and statisticians) and the scientists involved in basic biological and clinical mechanisms of disease [Hattis, 1987].

The promise of prevention that accompanies the new generation of biological markers is great. The reality, however, moderates some of the exhilaration or, at least, puts it in perspective. The major limitation is that few markers of disease have been validated. A broad front of effort is under way, but the products of this activity are not here as yet. Moreover, in some cases, validation will require time-consuming appraisals. By contrast, for markers of exposure, the picture is closer at hand. It is possible to identify some markers of exposure that are validated and, indeed, useful in assessing risk. The pioneer work of Calleman and Ehrenberg and colleagues [1978], using hemoglobin adducts, allowed for a risk assessment based on converting chemical dose to radiation equivalent dose; this approach identified the occurrence of excess leukemia risks in workers exposed to ethylene oxide years before they were demonstrated epidemiologically. However, the epitome of a biological marker—the binding of a xenobiotic to DNA (DNA adducts)—has not yet become the ultimate exposure marker or risk predictor that has been promised. Measurements of exposure have been clouded by unexplained interindividual variability. Other questions are also perplexing. Why, as Ashby [1987] pondered does a potent carcinogen, such as benzidine, yield relatively few protein adducts (22 pmol/gHb) compared with the weak carcinogen, methyl methane sulfonate, which yields relatively many (3,284 pmol/gHb) [Periera and Chang, 1981]? In theory, hemoglobin adducts are surrogates for DNA adducts. Another puzzling factor is that the same chemical can form different types of adducts; for example, a carcinogen can form adducts at different positions on DNA bases. The question is: Which of these is critical as an indicator of disease risk?

Another limitation to the promise of the current generation of biomarkers is that

most of the effects so far have been associated with carcinogenesis. Models for other toxic effects where biological markers exist have been slow being in developed or popularized. Exceptions include the areas of reproduction, immunotoxicology and, to some extent, renal and pulmonary toxicology. This should not be misconstrued as indicating a dearth of understanding of disease at the molecular level of other organ systems. This clearly is not the case; in fact, it is just the opposite. All medicine is moving toward a molecular understanding of disease. This is not as evident in occupational epidemiology which has been generally characterized, with notable exceptions, as the study of mortality. The promise of prevention will not become a reality without a concerted strategy for incorporating biological markers into occupational disease research. In developing countries, a key component of the strategy will be to find ways to transfer advanced technologies that are cost effective, practical, and appropriate.

TRANSITION FROM COUNTING BODIES TO COUNTING MOLECULES

If biological markers are to contribute to occupational health, they have to be shown to be valid indicators. Validity has a variety of definitions, but for this discussion, two are considered: laboratory validity and population validity. Laboratory validity is the characteristic of a marker assay or test system to be sensitive and specific [Griffith et al., 1989]. To be able to measure a marker or declare it absent, laboratory validity depends on the characteristics of the test (reliability, accuracy, precision) and on the biological characteristic of the marker. Population validity refers to how well the markers depict an event in a population. It does not matter how well you can measure a marker if there is too little to find among those being studied (i.e., in a particular sample from a population of workers). Hence, in assessing the validity of a marker in a population, it is necessary to consider its prevalence in the population. The prevalence affects the predictive value. It is distressing that some markers, despite high test sensitivity and specificity, will have little predictive value if they have a low prevalence in the study population.

A particular dilemma exists in terms of choosing the appropriate "gold standard" for validating markers of exposure, that is, in determining how well they indicate exposure or internal dose. If we decry ecological classification, even supplemented by personal breathing zone monitoring, and find markers that integrate over all routes of exposure and account for all manner of host factors, theoretically these markers then will be more representative of exposure than the ambient measures. But how do we test this? If efforts are made to evaluate the correlation between markers and ambient exposure, the two should not be correlated completely, since the markers are theoretically more accurate. One approach to developing validated markers of exposure may be to use controlled animal studies that restrict various host and ambient factors and allow for determining what changes occur in animals and with what dose. This information then can be considered in field studies of humans.

This suggestion points to a critical feature in biological marker research: the need for interdisciplinary research groups. This is most important in the validation and field-testing phases. Laboratory and field scientists must learn to communicate the concerns of each discipline, and to cooperate on attending to those concerns.

Validation studies of biological markers can be performed in occupational populations that have an increased risk of a toxic exposure or of disease. One suggestion

for such studies is to couple the marker validation efforts with ongoing programs of medical screening and biological monitoring. These provide a service for the population at risk and biological specimens for the researcher.

The pace of technological change in the area of biological-marker research is very rapid; thus, research strategies should be designed to accommodate this pace. Initial studies should be small-scale and flexible to incorporate tests for new markers and to discard tests found uninformative. Close communication between animal researchers and field scientists should aid in selecting the best markers and study designs and in developing standardized research.

IMPACT OF BIOLOGICAL MARKERS IN THE PRACTICE OF OCCUPATIONAL MEDICINE

Occupational medicine can benefit from the promised advances for prevention, environmental monitoring, and the evaluation of control technology that biological markers can provide. The occupational physician needs to have validated markers to use as tools in the assessment of individual workers or worker groups. Physicians may feel legal or corporate pressure to use markers that are not yet entirely validated. Here again, the need for interdisciplinary cooperation in the development of markers is evident. A cooperative process will provide an effective defense for clinicians in responding to pressures to utilize unvalidated markers. This is particulary true with regard to genetic screening and genetic monitoring. Genetic screening is the evaluation of current and future workers for biological markers of susceptibility. This is usually a one-time assessment to identify genetic susceptibility. Genetic monitoring is the periodic evaluation to detect markers of genotoxic effects. Very few genetic markers have been validated for use in genetic screening for occupational disease, but we are seeing the insurance industry poised to use them in setting individual policy rates [Schulte and Halperin, 1987; Hanke and Indulski, 1988].

Even if validated markers are available, a variety of ethical and legal issues will arise concerning their use. These are discussed later. Genetic monitoring depicts the dilemma that occupational physicians will confront for most biomarkers. What should be recommended when a preclinical change is found in a worker? Too often, pressures will be directed to altering more the worker rather than the work environment. Will our heightened ability to detect important biological changes lead to a discriminatory or punitive pattern for workers [Omenn, 1982; Murray, 1988]? The key to answering the question involves both biological and legal issues. Biologically, it is necessary to be able to distinguish adaptive markers from those representing maladaptive changes. This is part of what needs to be done in the validation process—a determination of whether a change is truly a critical effect. In the legal (or more precisely, the sociopolitical) arena, efforts need to continue to address issues ranging from rate retention for workers with an untoward finding to pressures for monitoring and follow-up for workers with a potentially deleterious biological marker [Ashford et al., 1990]. In countries in which there is no national health insurance, securing appropriate medical follow-up may be a problem. If the marker is not characterized as indicative of a disease, the worker will not be eligible for workers' compensation. On the other hand, insurers may contend that the marker represents a change brought about by employment, and hence, is not eligible for third-party coverage. The issue

is further complicated if both occupational and non-occupational factors can influence the appearance of a marker.

This leads to another impact the biological markers can have on the practice of occupational medicine. The detection and use of biological markers blurs the distinction between occupational and non-occupational medicine, because some markers can represent the effect of both occupational and non-occupational exposures, and some markers can be common changes for occupational and non-occupational diseases [Grieco, 1987; Zielhuis, 1985; Guidotti, 1986]. The occupational physician may be forced as Guidotti [1986] observed, to "take a comprehensive view of the health of the worker rather than to see through blinders that limit our vision to specific exposure and our response to a narrow range of administrative options." This is not an argument for the occupational physician to take on the responsibilities of the general practitioner, rather, as Guidotti [1986] argues, it represents an expanded vision of the occupational physician, and the provision of occupational health services from a position of understanding rather than from a position of censored ignorance. In other words, the use of biological markers will require occupational physicians to consider non-occupational factors, including genetic and medical history, diet, prescription drugs, smoking, and drinking, as well as occupational exposures.

Workers' compensation may also be affected by the use of biological markers in occupational research and practice. Much of the contentiousness of workers' compensation proceedings stems from issues of causation. Did the work cause (or exacerbate) disease? To the extent that biological markers can document specific exposures, internal dose, and body burden, they may be used increasingly in compensation proceedings. Eventually, this may put pressure on the use of ecologic classification of exposure to be supplemented by biological monitoring. Pressure may also be applied to increase the use of markers of susceptibility to explain differential distributions of disease.

Employing biological markers in occupational research or practice also presents a host of new obligations. In many cases, groups characterized by markers will not have "clinical" disease, but merely have a documented internal dose or a preclinical change. This may be a warning to institute preventive action, and it may require consideration of the need for ongoing monitoring, medical surveillance, or early treatment. Research using biological markers may have the effect of establishing ad hoc exposure, risk, or preclinical disease registries. Workers with these characteristics may be in a "never-never" land in terms of obtaining follow-up since, depending on the state of the law, they may be too early for workers' compensation. At the same time, private insurers may shun them because their "condition" is occupational. In addition, employers may be unwilling to maintain follow-up evaluation or will use the information in a discriminatory fashion, be it well meaning or nefarious. From the worker's perspective, the experience of any of these difficulties or the mere presence of some markers may be an impetus to bring about a lawsuit.

POPULATION THINKING

Much of the dilemma that confronts the user of biological markers in occupational health research and practice stems from the inherent biological variability between people. This variability is such that within the category of homo sapiens, it is unlikely, except for genetic twins, that any two people have the same genetic

makeup. The biochemical indivduality that people are born with is compounded by environmental differences and accrued life experiences [Hattis et al., 1987].

During this century, biologists have accepted the notion of biochemical individuality and rejected the notion of "essentialism" (the belief that everything is a product of a limited number of fixed unchanging forms). The term, "population thinking" represents this acceptance. As Mayr [1982] describes:

> Population thinkers stress the uniqueness of everything in the organic world. What is important for them is the individual, not the type. They emphasize that every individual in sexually reproducing species is uniquely different from all others, with much individuality even existing in uniparentally reproducing ones. There is no typical individual, and mean values are abstractions. Much of what in the past has been designated in biology as classes are populations consisting of unique individuals.

The question that might be asked is whether this view precludes statistical analysis of grouped data. Brain [1988] has observed that most statistical tests focus on measures of central tendency and their variability, and few focus on the extremes. He suggests that we need to develop techniques to determine the extent to which the variations seen reflect measurement error or true differences in susceptibility. Moreover, we may need to seek new means to accommodate the interpretation of biological phenomena at the molecular level.

Until recently, the analysis of variation at the DNA level was limited because the exact molecular structure of a lesion was not always apparent [Arnheim, 1988]. However, Saiki et al., [1985], described a new technology, the enzymatic amplification of DNA (termed DNA polymerase chain reaction). This is capable of increasing the amount of a selected target DNA sequence in a sample by enzymatically synthesizing many copies of the target DNA segment, allowing for an increased capability for identification. This technique will allow us to see more variation than we knew existed. We need to be able to describe this variation and then address it at a policy level.

For purposes of regulation, as in the environmental area, we may need to identify groups with biomarkers of susceptibility that need special protection. As Hornig [1988] concludes, "The central policy question is: Should variation in the sensitivity of groups and individuals be taken into account in occupational laws and regulations?" Samuels [1988] suggests that "We need to develop significant new tools in our struggle to manage populations at risk. . . . This need is based on the legacy that 'population thinking' leaves to risk managers." If every individual is unique, there is not a **typical** individual, especially when disease is being defined at the molecular level. He further decries: "Some will see this revelation as justification for excluding some men and women from work." Then he concludes, "that as an ethical axiom, we must treat all members of the population as if they are equally at risk and will inevitably suffer without intervention." Others, however, believe that the "sensitive" person at work should be regarded as handicapped. This would allow an individual the rights and protection afforded anyone with a widely recognized handicap. The newly passed Americans with Disabilities Act may be tested in this regard. The debate still continues.

There is little support for the view that the predominance of individual variation precludes statistical analysis of grouped data, or the ability to identify and manage high-risk subsets within occupational groups. Rather, it does provide an important

consideration that should be invoked in all statistical interpretations or risk management decisions where individual variability might be an issue.

ETHICAL AND LEGAL ISSUES IN USING BIOLOGICAL MARKERS

Although biological markers provide tremendous opportunities for disease prevention, their use also raises a number of additional ethical and legal issues and new responsibilities [Ashford, et al., 1990; Schulte, 1987; Rothstein, 1984]. These issues can be discussed in the context of marker development and marker use. When developing and validating markers, research involving animals is required. Such research is of great benefit to human health and should be continued. However, care should be taken that marker research is performed, in a peer-reviewed fashion, on animal models appropriate for the development of a marker and extrapolation of the results to humans. During field tests using unvalidated markers, how should the state of knowledge about the markers be reported accurately to subjects when securing their consent to participate? In developing study protocols, what actions will be taken for people with extreme results? In general, subjects should be notified if subsequent research identifies a predictive risk associated with markers that are used in validation studies. At the end of the studies, subjects should be informed of results. Thought needs to be given about informing subjects of study results involving markers that can be construed as early disease and that can inadvertently trigger statutes of limitation considerations related to compensation issues. Finally, the collection and handling of biomarker data should adhere to good practices for privacy and confidentiality.

The potential for the unethical use of biological markers is great. This issue has been raised most pointedly with markers of susceptibility that might be used *in* genetic screening [Schulte and Halperin, 1987; Hanke and Indulski, 1988]. If these markers correlate with particular racial or cultural characteristics, the potential exists that individuals and groups, already burdened by discrimination, may face further burdens. In addition, because of individual variability, there may be a false assurance that workers who "pass" such screening tests will constitute a hardier group, and, thus, the temptation to place them in the most hazardous jobs or to relax controls might increase.

The intentional or an inadvertent disclosure of the findings of research or practice involving markers of exposure, disease and susceptibility could have a chilling effect on a worker's ability to get or keep jobs, or to obtain health insurance. A major issue is what to do with employees who manifest altered markers in the absence of diagnosed disease. Findings of workers with excess frequencies of various markers may put an ethical obligation on employers to provide follow-up monitoring. In terms of workers' responsibilities, the question arises about whether or not they have a responsibility to disclose the results of marker evaluations performed on them to insurers or potential employers. The use of biological markers in occupational health also must be considered in terms of worker monitoring. Two legal issues have emerged: the rights of those monitored and the use of monitoring as a primary control strategy.

Ashford et al. [1990] and Rothstein [1984] have comprehensively identified many issues surrounding the rights of monitored workers. Ashford et al. [1990] concluded that, "discriminatory practices and consequential tort suits, anti-discrimination suits, deterioration of labor–management relations, and agency sanctions may

follow poorly conceived and poorly executed human monitoring." They believe that when the costs of worker removal are fully internalized in costs of production, monitoring for biological markers as a primary control strategy will not be as economically attractive as proponents have argued. That debate still continues.

Generally, the use of biological markers in monitoring has been considered as part of a continuum of protective meaures, and such monitoring should be used only after primary prevention by environmental control and substitution has been applied [Halperin et al., 1986]. Still, as we understand more about disease at the molecular genetic level, the choice of appropriate strategies becomes less clear.

CONCLUSION

The use of biological markers in occupational health research and practice is now occurring, and it is inevitable that this usage will increase. These markers are of great promise, but their development and use require asking fundamental questions about what it means to be human, to be different, and to be at risk. We must resist the arrogance that comes from thinking that by being able to measure something we have understood it, and that only research at the molecular level is worthwhile. The morbidity and mortality studies that have provided great gains in occupational health are still needed and will continue to provide leads and answers. We must resist the temptation to think that the only useful information from workers will come from the measurement of a biological specimen rather than from paying attention to what workers say, as well as, their social, cultural and political milieus.

With these caveats, there should be a redoubling of efforts to realize the promise of biological markers. Professional training should stress interdisciplinary collaboratory. Epidemiology and industrial hygiene curricula should include more basic biological science with emphasis ranging from molecular biology to pharmacokinetic modeling. More integrated studies involving the testing of markers, first in laboratory animals and then in humans, should be commissioned. Preemptively, ethical and legal considerations need further study and evaluation.

Ongoing efforts of marker validation should be developed. These efforts should include the banking of specimens and making them available for research. Clinicians should be encouraged also to provide specimens for banking and future research. Biologically based indices should be more widely considered in the regulatory arena. Methods for intervention in high-risk groups should incorporate biological monitoring for risk assessment and in the determination of the effectiveness of interventions. Understanding of occupational disease at the molecular level will continue to grow at a rapid pace. We have no choice about this. The choice we do have is to anticipate the ethical and legal implications of this capability, to guide the technology, to realize the promise. In short, occupational health can reap the benefits of the current advances in biological understanding, but it will take a concerted and cautious effort.

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