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Interpretation and Communication of Molecular Epidemiologic Data

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Practitioners of molecular epidemiology are likely to be of laboratory or epidemiologic disciplines. In neither case are they likely to be trained in effective risk communication procedures; indeed they may not even relish such actions. Nonetheless, as in all epidemiology, molecular epidemiology is a part of public health. Thus, it is a discipline that involves human subjects and is targeted directly to making a difference in the health of populations. Hence, molecular epidemiologists must be able to interpret and communicate their results with some proficiency.

The interpretation and communication of molecular epidemiologic results is the responsibility of researchers. It begins with the recruitment of subjects. Patients and research subjects have a right to give informed consent when participating in molecular epidemiologic research. The Nuremberg Code and the Helsinki Convention affirm and reaffirm the right of an individual to be given full disclosure about potential risks and benefits of experimental biomedical procedures (Duncan *et al.*, 1977). These principles might be extended to cases in which researchers have information about potential health risks within identifiable populations (National Commission, 1978; Schulte and Ringen, 1984; Gordis, 1991; Lerman *et al.*, 1991; Schulte, 1991). In these situations, subjects may be able to claim a "right to know" assay and study results. This "right" is based on the view that the right to self-determination is a fundamental democratic principle. In this context, individuals are considered best able to protect their health, lives, and interests if they are informed about a known risk. When the meaning of molecular epidemiologic information is uncertain, the required actions are less defined and more of a problem exists in communication of the information. Issues

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pertaining to the interpretation and communication of molecular epidemiologic information are discussed in this chapter.

Interpretation

The use of biologic markers in epidemiologic research presents some unique issues regarding the interpretation and communication of results. These issues can arise for markers of exposure, effect, and susceptibility, but are more prevalent for the latter two, especially in studies in which the health risk associated with a marker is not known. Until the sensitivity, specificity, and predictive value of an effect marker are known, it is probably more practical to consider it an indicator of exposure rather than of effect. Markers of susceptibility also present major challenges to interpretation and communication. Widespread use of these markers may have ethical and legal implications that include discrimination in employment or obtaining insurance, and may be used to trigger litigation or requirements in laws pertaining to reporting of health effects.

Questions of interpretation also arise for markers of exposure. For example, how is the contribution of DNA adducts from an environmental hazard distinguished from those from a home hobby? To what extent does a DNA adduct constitute DNA damage? Most markers of exposure can have an implied if not explicit risk interpretation, but the researcher may be uncertain about the meaning or unwilling to push the interpretation to the level of implication for a subject's health.

Generally, subjects may accept that a study only asks a research question or that the investigator is uncertain of the findings. Still, when biomarkers are used in studies of controversial topics, investigators may have to take extra time to discuss results with subjects or community groups. To avoid or reduce confrontational reactions by subjects and affected groups, it may be necessary to involve them in the planning of investigations rather than simply communicate results to them.

Much of the uncertainty in molecular epidemiologic research derives from the newness of the field and the inherent qualities of biologic markers, such as variability, the fact that they are individual-specific measures, and the expectations of research subjects to want definitive answers. These issues will be discussed in subsequent sections.

Variability of Results

Within groups of subjects, early research using biologic markers has shown great variability in results. All interpretations will be influenced by how well sources of variability can be identified and accounted for. Biologists long have recognized this inherent variability among individuals (Mayr, 1982).

With the exception of identical twins, no two people have the same genetic make-up.

In 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) (Mayr, 1982). "Population thinking" is a phrase that has been used to represent 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.

One might question 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; few tests focus on the extremes. He suggests that we need to develop techniques to determine the extent to which observed variations reflect measurement error or true differences in susceptibility. Moreover, we may need to seek new means to accommodate the interpretation of biologic phenomena at the molecular level.

In practice, these views should not preclude statistical analysis and interpretation of biomarker research. However, they should serve as warnings for researchers to design studies that account for major sources of variability and to evaluate research to determine whether this has been done. If it has not, appropriate caveats or alternative interpretations should be included.

Group Results Compared with Individual Results

Interpreting studies with biologic markers has proved difficult for other reasons also. The traditional paradigm that epidemiologic research pertains to a group leaves individual study subjects at a loss regarding the meaning of results for them. Subjects may be able to learn about significant group risks, but may not be able to obtain any meaningful information about individual risk unless investigators have developed risk functions that will calculate individual risk. Still, institutional review boards often require that study subjects receive their own test results along with some explanation or interpretation. Epidemiologists have come to no agreement about the language for these communications.

One of the major potential advances of molecular epidemiology is the ability to obtain individual-specific information that may be predictive of risk (Albertini *et al.*, 1991; Shields and Harris, 1991; Thilly, 1991). This ability is not new to epidemiologic research (e.g., Truett *et al.*, 1967), but the exquisite sensitivity of individual risk functions based on gene assessments

puts researchers and society in difficult positions with respect to interpretation of results, privacy, and confidentiality.

Subjects may misconstrue the purpose of research and reduce the research question to whether or not they are "all right." Clearly, this attitude could pose a problem in most biomarker studies that may assess only a marker's validity in providing information that is useful in an epidemiologic, rather than a clinical, sense (Schulte and Singal, 1989). However, some biomarker studies may identify clinically relevant findings.

Any positive study that uses markers that are considered biologic changes capable of being part of a disease process should trigger considerations of the need for medical surveillance. Although this is a prudent policy that may involve surveillance of some subjects with false-positive test results, it will at least allow for identification of early disease in subjects who are candidates (true positives) for early intervention or therapy. Beyond that, researchers still should make a strong effort to describe the limitations of biologic markers, to counsel subjects, and, in some cases, to provide the subjects' personal physicians with information regarding the state of knowledge about the markers. One suggestion for handling uncertainty in molecular epidemiologic research is to couple such research with conventional screening of high-risk groups (Schulte, 1986). At a minimum, this alternative offers the opportunity to provide study subjects with some information (acquired from the conventional screening) that can be interpreted with a known degree of certainty. In such a setting, people often are willing to provide additional specimens for research purposes.

Of highest importance to study subjects and the general population is whether or not epidemiologic information indicates disease risk. Technically, this describes the question of predictive validity discussed in Chapter 3. What is the predictive value of a marker assay? This question pertains primarily to markers of effect and susceptibility. The predictive value of an assay is often misinterpreted because it is presented as a percentage (Gambino, 1989). As Gambino notes,

> It is intuitive to assume that low percentages (70% or less) are bad and high percentages are "good." A positive predictive value of 20% was cited as proof that a test should not be used even though the positive likelihood ratio for the same test was 50. A likelihood ratio of 50 means that the posttest odds will be 50 times higher than the pretest odds of disease. Now that is a large increase in the odds.

In a molecular epidemiologic study, typically only one or few markers are used. A single marker assay rarely should be interpreted in isolation. On an individual basis, the findings should be confirmed by a repeat test given at some later date. Other confirmatory studies should be sought for group results. When possible, batteries of markers may provide a fuller picture than would be seen with one or a few markers.

A danger exists that molecular epidemiology practitioners or, more

likely, those in the public or media who interpret such research will be misled by the exquisite sensitivity of some assays to believe that the assays have, for example, identified conclusively a person who has incurred a gene mutation as the result of environmental or occupational exposure to mutagens. Until these findings are validated and the predictability of the marker assessed, indefinite interpretations can cause a range of problems for the individual and the society.

Validated and invalidated marker results can present a variety of societal problems for study subjects. Individuals correctly or incorrectly classified in the tails of a distribution of marker frequencies may be in danger of prejudice and discrimination in terms of insurance, job security, and obtaining loans, and at risk of negative interpersonal responses [Office of Technology Assessment (OTA), 1990; Ashford, 1991; Weatherall, 1991].

To reduce these untoward reactions, it is incumbent on researchers to take care in interpreting and communicating molecular epidemiologic research and, moreover, to anticipate untoward use of such research and participate in societal discussions of such questions.

Communication

Molecular epidemiologic information may need to be communicated to study subjects in at least three different instances as well as to the general public and to patients in clinical settings.

Study Subjects

The three instances in which study subjects may need molecular epidemiologic information are (1) during recruitment when obtaining informed consent; (2) when communicating biomarker test results; and (3) when communicating molecular epidemiologic study results.

Obtaining Informed Consent

The process of communicating information from molecular epidemiologic studies actually begins with the recruitment of subjects. A review of informed consent of hospital patients who participated in research demonstrated that they had low levels of recall, understanding, and knowledge subsequent to the administration of informed consent (Silva and Sorrell, 1988). The reasons given for this lack of comprehension involved clarity, language, and formats used. The ethical principle underlying recruitment of subjects into research studies is that the participants should be provided with a true understanding of what the study entails, the benefits to be derived, and the risks involved. It has been argued that candidate subjects for molecular epidemiologic studies rarely will be able to give truly informed consent because

of the complexity of the research and because the researchers themselves are uncertain about the meaning of potential results (Samuels, 1992).

Maximizing the understanding of potential study subjects could result in increasing selection or volunteer bias. However, in a democratic society, this is the cost of contemporary research. Researchers may need study designs to balance such bias among study groups.

Communication of Test Results

Researchers display a difference of opinion about whether the results of biomarker tests should be communicated to study subjects. Some researchers, institutions, and Institutional Review Boards (IRBs) require such communication whereas others do not. When communication is required, an approach sometimes used provides individual results and the average for the group. An example is shown in Figure 9.1.

Although the letter satisfies the spirit of communicating results in a relatively clear manner, it still is quite technical. The problem for research communicators is the implied tension between the need to communicate complex results in an understandable manner and the potential liability of not providing complete information. Communications experts would recommend a brief bulleted message over the letter with its caveats, footnotes, and technical terms. How does the researcher balance these pressures? Certain features in the letter represent attempts to overcome the dilemma of trying to communicate complex molecular epidemiologic data. These features include striving to use simple language, giving group comparisons, putting results in the context of an occupational health standard, and, most importantly, giving a contact person for follow-up discussion.

During the recruitment phase, the participant in a molecular epidemiologic study should be informed of the extent to which the marker assays will reflect individual health. Most molecular epidemiologic studies will have little information about a subject's health. The purpose of such studies may be to validate a marker or elucidate a mechanism; only with validated markers will studies show an association indicative of increased risk of disease [National Research Council (NCR), 1991]. Still, subjects may forget this fact between the time they sign the informed consent document and the time they receive test results. At that time, they generally are interested in knowing whether they are "all right" or have any problems. Because of the limitations or purpose of the study, such information generally cannot be determined from biomarker assays. Some studies may be performed only to confirm exposure, for example, by detecting DNA adducts.

Assays may have various limitations that should be mentioned when informing subjects of results. Since biomarkers often reflect exposures over multiple routes and from different sources, it is important to describe these possibilities to account for variation in findings. Marker results may be confounded or modified by exposures or conditions not actually part of a study.

FIGURE 9.1 Example of a letter notifying subjects of the results of molecular epidemiologic test

Date

Dear _____.

Thank you again for participating in the medical study on ethylene oxide exposure. Your individual results from the laboratory tests on your blood are shown below. These results were delayed because they were done in various countries, and some of the tests took longer than expected. The final report of group results will be sent to you in a few months.

As you know, the study was done to see if measurements of ethylene oxide in red blood cells and changes in the genetic material of white blood cells are related to a person's work exposure to ethylene oxide. The measurements of ethylene oxide in red blood cells are called hemoglobin adducts and the genetic changes are called sister chromatid exchanges, chromosomal micronuclei, and HPRT mutations. We compared a group of workers with exposure to ethylene oxide (sterilizer workers) to a group of workers with no ethylene oxide exposure (other hospital workers). We believe that workers with ethylene oxide exposure will have more of these changes. In the following table, your results are shown along with the average values found in each of these two groups:

		Worker group	
	Your results	Sterilizer workers	Other hospital workers
Hemoglobin adducts[a] (Average number in moles per gram)	0.17	0.13	0.07
Sister chromatid exchanges[b] (Average number per cell)	7.22	6.15	4.93
Chromosomal micronuclei[c] (Average number per cell)	1	0.74	1
HPRT[d] (Number of "mutations")	112×10^{-6}[e]	124×10^{-6}	724×10^{-6}

[a]Hemoglobin adducts are attachments of environmental molecules, in this case ethylene oxide, to the hemoglobin molecule.
[b]Sister chromatid exchanges occur when pieces of chromosomes are exchanged from one chromosome to another.
[c]Chromosomal micronuclei are pieces of chromosomes found in cells.
[d]HPRT is the abbreviation for a gene on the X chromosome.
[e]"$\times 10^{-6}$" means "times one one-millionth."

Hemoglobin adducts of ethylene oxide apparently are found in everyone, and may be due to cigarette smoking or even produced naturally in humans. In order to see how well hemoglobin adducts are associated with exposure, we compared workers with ethylene oxide exposure to those without such exposure. It is not known if the presence of an increased amount of hemoglobin adducts or of the chromosome and gene changes increases a person's risk of disease. This was not the intent, and it cannot be determined in this study.

Additionally, we have measured the potential exposure to ethylene oxide among employees in your department. At least some of the measured exposures in your department were above the NIOSH recommendation for exposure to EtO. All measured exposures were below the Occupational Safety and Health Administration (OSHA) federal standard for exposure to EtO.

If you wish to discuss these results further, please call me at (phone #) or send inquiries to me at the following address: (address)

Sincerely yours,
Study Investigator's Signature

An example of how confounding influence can be addressed is seen in the following excerpt from test-result notification (Schulte and Singal, 1989):

> The type of semen quality changes observed in this study can be found in everyone and happen for a number of reasons. Some of these reasons have been linked with human health problems and some have not. Factors in everyday life, like smoking and

> the use of certain medications, can also change semen quality measurements. There are also day-to-day changes in measures of semen quality.

Some assays cannot be interpreted easily because they are research tools and have no established normal range. This fact was expressed in one results letter (Schulte and Singal, 1989) in the following manner:

> We should comment upon the source of the "normal" or reference range for tests. For some tests the reference range is listed as N.A. (not available). Usually these tests are research tools for which reference ("normal") values have not been well established. Research tests provide useful information about groups of workers, but the results are difficult to interpret in individuals. Other tests, such as urine creatinine, are used mainly to standardize other tests and are not meaningful themselves. We report the results for your information but do not comment on them.

The inability of a research test to predict disease generally should be expressed with no attempt to blur the uncertainty. An example (Schulte and Singal, 1989) is a study involving exposure to 4,4′-methylenebis(2-chloroaniline) (MBOCA), a suspected bladder carcinogen, in which subjects were administered both the routine Papanicolaou cytology test and the experimental quantitative fluorescence image analysis test. The letter read:

> QFIA (Quantitative Fluorescence Image Analysis) measures the amount of genetic material in cells, and may detect cells which have an increased content of genetic material. Increased content of genetic material is one difference between tumor cells and normal cells. QFIA is an experimental test, and we still don't know its value in predicting who is likely to get bladder cancer.

Researchers quite often may be uncertain about the meaning of biomarker assays. Not to communicate the true extent of uncertainty about assay results may be unethical. It is important to communicate test results to provide information to the study subjects and to do it in an informative and understandable way.

Communication of Study Results

Perhaps the most important information to communicate are the overall results of the study after assessing the association between exposures and outcomes. At this stage, the researcher can attempt to explain the results. For molecular epidemiologic results, despite the collection of individual samples, the results still may be group specific and not indicative of risk on the individual level. However, if an individual risk function is calculated, as with lipid and other risk factor information in multivariate models of cardiovascular disease or with assays for a particular gene mutation, it may be possible to describe individual risk (Truett *et al.*, 1967; Shields and Harris, 1991). Nonetheless, disclosing group results can be beneficial to subjects by providing them with general risk information about an environmental or occupational hazard. Group information also provides a framework for subjects to know the extent of a troubling finding, that is, it may provide a perspective.

For test and study results, researchers may bear a responsibility to warn subjects of the need for a preventive action or to recommend ongoing monitoring, medical surveillance, or early treatment. Research that uses biologic markers may have the effect of establishing ad hoc "exposure," "risk," or preclinical disease registries (Samuels, 1982; Schulte *et al.*, 1986; Schulte and Kaye, 1988). Whether or not these registries are maintained will depend on the availability of funds, the political will of the registry members, and the interests of the investigator. Generally, it is not current practice to maintain such registries, although federal law (CERCLA, PL 96-510) has prescribed the formation of "exposure registries."

The communication of study results that indicate risk to a cohort may define and highlight a high-risk group in society (Schulte and Ringen, 1984; Schulte 1986). This label has various meanings to different sectors of society. To the subjects, it has the exaggerated meaning that they are entered into a lottery involving their health. Some individuals may be able to put a balanced perspective on this knowledge; others may need additional counseling or support. All may need certain periodic medical surveillance to determine whether or not they have developed signs of the disease for which they are at risk. The ethical responsibilities of researchers and research institutions (including corporate research groups) are only beginning to be well delineated. However, some useful models can be considered (Fischhoff, 1987; Murray, 1988; Lerman *et al.*, 1991; Sandman, 1991).

General Public

Researchers who publish and otherwise disseminate molecular epidemiologic information to subjects may be called on to interpret the meaning of such findings for the general public. When validated markers are available, molecular epidemiologic information may be able to provide individual risk information (Shields and Harris, 1991). When communicating molecular epidemiologic information, care should be taken to distinguish between validated markers and those not yet validated. The current state of research in this field is, essentially, one of validating markers, not of identifying etiologic factors or conducting risk assessments.

For communication of molecular epidemiologic information to be effective, it must comply with established principles of risk communication. These principles include viewing risk communication in the framework of risk management and demonstrating sensitivity to the needs and reactions of the involved parties. Molecular epidemiologic information often contains elements that will be provocative to the general population. Thus, terms such as "mutation," "gene rearrangement," or "DNA adduct" conjure up meanings and fears that may not be warranted by the actual research. The normal background frequency of spontaneous mutations in the genome and the extensive capacity for repair (see Figure 9.2 and Table 9.1) often are not consid-

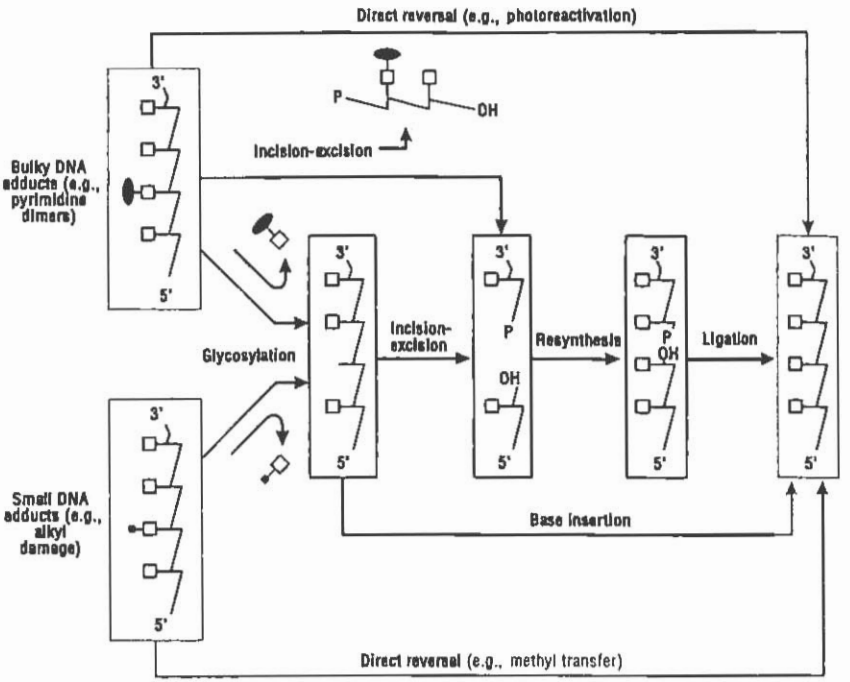

FIGURE 9.2 Schematic outline of some of the major pathways of DNA damage repair. (Reprinted with permission from Vijg *et al.*, 1986, in Baan, 1987. Copyright © 1987 by Springer-Verlag.)

ered when the public hears a message about a molecular epidemiologic study involving measures of mutations or DNA adducts.

The complexity of molecular epidemiologic information perhaps will make the information harder to convey than the usual outcomes of epidemiologic studies. Because molecular biologic research is proceeding so rapidly, it is unlikely that the general population understands the basic principles of cell growth and regulation against which to evaluate a communication.

The results of molecular epidemiologic studies are likely to involve the impact of genetic *and* environmental factors in disease. In discussions of environmental disease, it has been difficult to address genetic risk factors since there have been tendencies to put the emphasis either entirely on the genetics (and blame the victim) or entirely on the environment. For most diseases, a combination of endogenous and exogenous factors is likely, so risk communications must be performed within these parameters. Molecular epidemiologic research does have the potential for clarifying the "nature–nurture" debate, but such clarification still taxes risk communicators.

In "Monitoring the community for exposure and disease: Scientific, legal, and ethical considerations," Ashford *et al.* (1991) identified many of the

TABLE 9.1 **Estimated DNA Damage Rates and Repair Rates in Human Cells at 37°C**

Damage				Repair	
Endogenous	**No./hr**	**Exogenous**	**No./hr**	**Type**	**No./hr**
Depurination	580	Pyrimidine dimer formation (noon Texas sun)	$.5 \times 10^4$	Single strand breaks	2×10^5
Single strand breaks	2300			Thymine glycol removal	10^5
		Single strand breaks		Pyrimidine dimer removal	
O^6-Methylguanine formation	130	(background radiation)	10^{-4}	Normal cells	5×10^4
				XP C cells	5×10^3
Thymine glycol formation	13	Thymine glycol formation (background radiation)	10^{-5}–10^{-4}	O^6-Methylguanine removal	$\sim 10^4$

Source: Reprinted with permission from Setlow (1988).

issues pertinent to molecular epidemiology practice and information dissemination. These authors and others (Schulte, 1987; OTA, 1990; NRC, 1991) have addressed this topic and drawn the following conclusions.

- Molecular epidemiologic data should have a relatively large signal-to-noise ratio, that is, there should be as little ambiguity as possible that the "effect" found is above a background rate.
- Communication of molecular epidemiologic information to a community cannot be separated from the social or political use of the data.
- Dissemination of risk information from molecular epidemiologic studies has implications for citizens' and employees' rights to privacy, confidentiality, and nondiscrimination with respect to employment, insurance, and acceptability for loans.

The Centers for Disease Control/Agency for Toxic Substances and Disease Registry [Centers for Disease Control (CDC), 1990] established a subcommittee to review currently available laboratory tests for their suitability to measuring human organ-specific biomarkers. They concluded that:

> . . . when a biomarker is included in a study, it must be evaluated against established batteries of biomarkers. A separate statistically valid evaluation of the new marker must be conducted. The marker assay results produced in this evaluation should be used only for marker description and evaluation, and they should not be presented to the study subjects as individual marker assay results until all relevant data have been compiled and reviewed. Results released before the physiologic significance of the marker is thoroughly assessed could cause unnecessary public alarm and spur demand for the test before the meaning of the results is fully understood. (CDC, 1990)

The subcommittee also concluded that the evaluation process to find new markers should be conducted anonymously, with informed consent of the subjects and coding of specimens to delete identification of all study subjects. Before a test is considered to have completed the investigative phases, the biochemical or physical abnormality associated with the marker should be identified, and the probability that the abnormality will progress to disease as well as the nature of that disease should be known (CDC, 1990).

Various government agencies, universities, and corporate researchers have an array of practices (CMA, 1991). The National Institute for Occupational Safety and Health routinely informs subjects of molecular epidemiologic studies of all test and study results.

The societal response to people with "abnormal" levels of markers can give rise to ethical issues pertaining to discrimination, need for medical follow-up, and removal of workers or residents from areas of imminent danger (Schulte, 1987, 1991; Rothstein, 1989; Ashford *et al.*, 1990). The question is whether people with a certain biologic marker of susceptibility have rights to protection against discrimination as do people with more visible physical handicaps (Rothstein, 1989; OTA, 1990). Increasingly, these types of questions will be asked by individuals who live or work near hazardous

waste sites, and who receive biologic monitoring as part of an epidemiologic study or a routine medical surveillance.

The interpretation of biologic monitoring data also can impact litigation concerning alleged health effects and exposure to such environmental concerns as hazardous wastes. Ashford *et al.* (1990) assert that human monitoring data have the potential to bring about a change in the nature of evidence used in such cases.

> Typically, the evidence offered to prove causation in chemical exposure cases is premised on a *statistical* correlation between disease and exposure. Whether the underlying data are from epidemiologic studies, toxicological experiments, or the results of a complicated risk-assessment model, they usually are *population*-based. This places the plaintiff at the mercy of the attributable risk (expressed as the percentage of cases of the disease attributable to the exposure) for the study population. Unless the attributable risk is greater than 50%—that is, unless the incidence rate among those exposed to the chemical is more than double the background rate—the plaintiff cannot prove, *on the basis of the available statistical evidence*, that it is more likely than not that his or her particular case of the disease was caused by the chemical exposure.

Responsibilities of Molecular Epidemiologists

Sandman (1991) has identified communication responsibilities of epidemiologists that apply to molecular epidemiologists as well:

1. Tell the people who are most affected what you have found—and tell them first.
2. Make sure people understand what you are telling them, and what you think the implications are.
3. Develop mechanisms to bolster the credibility of your study and your findings.
4. Acknowledge uncertainty promptly and thoroughly.
5. Show respect for public concerns even when they are not scientific.
6. Involve people in the design, implementation, and interpretation of the study.
7. Decide that communication is part of your job, and learn the rudiments.

Clinical Settings

Genetic and cancer-risk counseling are representative of areas in which molecular epidemiologic information may be communicated presently and in the near future (Weatherall, 1991). In these areas, little is known about the impact of the communication, but there is great potential for help or harm. By communicating molecular epidemiologic information in clinical settings, it is possible to motivate high-risk individuals, for example, to adhere to cancer prevention and surveillance recommendations or to make informed de-

cisions about family planning. However, these communications may have adverse psychological and social consequences (Lerman *et al.*, 1991). Notification of cancer risks that involve genetic susceptibility and environmental exposures—in whatever proportions—are fraught with ethical dilemmas. For example, how do you tell a person that he or she is genetically susceptible to a particular disease? What kind of follow-up, support, and counseling should be anticipated? As Lerman *et al.* (1991) note,

> Nonmaleficence, or obligation of health professionals to do no harm, also is one of the cornerstones of ethical practice. For example, without an action plan for avoiding negative psychosocial sequelae, the mere transmittal of genetic information could cause more harm than good—particularly if no known means are available to reduce risk. This may differ from decisions to communicate to study subjects who have a right to know of test and study results. There too, however, anticipation of untoward effects should be considered.

Banked Specimens

The collection and storage of biologic specimens for future molecular epidemiologic research presents unique communication issues. Initially, there is the question of whether specimens can be used for a purpose or assay different from the one for which they were collected. This question has not yet been widely addressed. Initial discussions in the early 1980s by an ethics subcommittee of the CDC (CDC, 1983) suggested that the use of such specimens for purposes other than those for which they were collected is unethical. Does a broad informed consent statement, such as "Specimens will be stored for additional cancer studies as assays are developed," provide adequate information to subjects from which to make a judgment to allow future assays? Despite the extent of specimen banking worldwide, this question has not been addressed completely in the ethical or scientific literature.

Other questions discussed in this chapter need to be considered with respect to research on banked specimens. Who owns the specimens and, by extension, who owns the human genome (Weatherall, 1991)? To what degree are researchers responsible to communicate results to subjects who provided specimens years earlier? What if, in the intervening years, the marker that was studied originally is found to be predictive of disease? Is there an obligation to inform subjects who gave stored specimens? Many of these questions have not been addressed and will confront researchers in the near future.

Two principles seem to cover this type of research: (1) When researchers obtain health risk information from a molecular epidemiologic study, they have a responsibility to communicate the information to subjects. (2) When collecting biologic specimens for banking, researchers should indicate in the informed consent process the fact that specimens will be banked as well as the range of research that might be conducted.

Access to banked specimens for research should be controlled. When informed consent does not seem to cover subsequent research, one possible solution is to convene a surrogate committee to represent interests of subjects and other parties, to review research proposals, and to determine the extent to which efforts should be made to go back and inform subjects. Subsequent research on banked specimens should adhere to current accepted practices for maintaining confidentiality and privacy of subjects.

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Molecular Epidemiology

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