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Biological Markers in Tort Litigation

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Abstract. Epidemiologic studies provide quantitative information about the pathologic role of a single risk factor in large populations, but available biostatistical data are not sufficient to apportion liability when exposure to more than one potential risk factor has occurred. Given this scientific void, some courts, upon a threshold demonstration of negligence, have shifted the burden of proof regarding causation to the defendant—forcing him to prove a negative—that he did not cause the plaintiff's injuries. To the extent biologic markers become a scientifically acceptable and legally reliable means of proving that exposure to a particular risk factor caused a specific disease, judicial decisions regarding disease causation can be made with scientific certainty and without subjunctive reference to the defendant's purported negligence.

Key words and phrases: Biologic markers, epidemiology, multivariate analysis, probability of causation, evidentiary reliability, burden of proof, tort litigation.

Forensic attempts to substantiate or refute an asserted causal relationship between a plaintiff's toxic exposure and the manifestation of a latent disease are usually based upon epidemiologic studies. Although such studies may provide useful quantitative information about the pathologic role of a single risk factor in a large population, generally they do not provide an empirical predicate for multivariate analyses specific to the individual plaintiff. This axiom is one of the primary sources of uncertainty in the recent federal effort to develop radioepidemiologic tables reflecting the probability of cancer induction due to differing circumstances of ionizing radiation exposure. If a person has been exposed to more than one risk factor, there is not sufficient epidemiologic data to calculate the probability that one particular risk factor caused the disease. The National Institutes of Health (1985) committee of eminent scientists who developed the tables candidly acknowledged:

> A person with a malignant neoplasm of a kind that can be induced by radiation may have a history not only of radiation exposure, but also of exposure to other carcinogens that may be significant with respect to that particular cancer. Cigarette smoking or benzene exposure are examples. The PC (probability of causation methodology) has been defined as being conditional upon individual characteristics, among which are included other carcinogenic exposures, but it may vary depending on the presence (or absence) of exposure to other carcinogens.

It is not possible to modify the PC formula to account for every possible exposure that can be listed. For example, prolonged exposure to inhaled asbestos fibers is a risk factor for lung cancer and for mesothelioma. Although mesothelioma has not been shown definitely to be induced by ionizing radiation, lung cancer has. If possible, therefore, it would be desirable to take explicit account of the possible role of asbestos exposure in the causation of a lung cancer in, for example, a shipyard worker who had radiation exposures while working as a radiographer examining welds, who also had spent several years installing asbestos insulation, and who smoked two packs of cigarettes daily. It is impossible to undertake so complete an analysis at this time, because data concerning such combined exposures are not available, and further because we are not yet able to classify asbestos exposures adequately with respect to lung cancer risk in relation to duration and intensity of exposure or exact type or fiber size of mineral.

Indeed, one National Academy of Sciences (1984) committee recently concluded that "... for a specific person we have no way to apportion blame to causes through verifiable measurements and outcomes in that person."

This scientific deficit notwithstanding, before assigning "blame" to a particular risk factor, tort law

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(American Law Institute, 1965) plainly requires an assessment of: (a) the number of other factors which contribute in producing the harm and the extent of the effect which they have in producing it; (b) whether the actor's conduct has created a force or series of forces which are in continuous and active operation up to the time of the harm, or has created a situation harmless unless acted upon by other forces for which the actor is not responsible and (c) lapse of time.

The consensus that cancer has multiple causes, that both initiating and promoting agents are implicated, and that cancer is characterized by long latency periods, underscores the significance of the scientific deficit and the legal requirement. This incongruence between the known and that which yet must be learned has sponsored several subjunctive perspectives inimical to the just resolution of toxic tort litigation. One court (*Allen v. United States*), for example, to find a nexus between radiation exposure and disease, discounted the traditional concept of statistical significance:

> The cold statement that a given relationship is not "statistically significant" cannot be read to mean "there is no probability of a relationship." Whether a correlation between a cause and a group of effects is more likely than not—particularly in a legal sense—is a different question from that answered by tests of statistical significance, which often distinguish narrow differences in degree of probability.
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> The value of the available statistical data concerning radiation and cancer . . . is not confined by arbitrary tests of "statistical significance." Nor is the court constrained by simplistic models of causal probability impressed upon the judicial "preponderance of the evidence" standard.

This occurs because courts are understandably better prepared to adjudicate negligence rather than causation in toxic tort cases involving biostatistical dilemmas. Thus, judicial decisions may well reflect the relative negligence of the tortfeasor rather than the scientific probability that his act caused harm. In the legal decision discussed above, the court essentially shifted the burden of proving causation from the plaintiffs to the defendant after the plaintiffs established the defendant's negligence to the court's satisfaction:

> Where a defendant who negligently creates a radiologic hazard which puts an identifiable population group at increased risk, and a member of that group at risk develops a biologic condition which is consistent with having been caused by the hazard to which he has been negligently subjected, such consistency having been demonstrated by substantial, appropriate, persuasive and connecting factors, a fact finder may reasonably conclude that the hazard caused the condition absent persuasive proof to the contrary offered by the defendant.

It is commonplace that if the scientific community cannot perform the multivariate analysis necessary to apportion blame, neither can the legal system.

There is, however, research in progress which portends a legally and scientifically acceptable method of allocating liability for toxic harm. The legal requirements to be met by such a method have been discussed above. The scientific requirements have been derived by Dr. William G. Thilly (1986), Professor of Genetic Toxicology at the Massachusetts Institute of Technology, from Ferdinand Koch's classical postulates: In order to prove that an agent has caused biologic change in an individual it is necessary to show that (a) the person has been exposed to an amount of the agent sufficient to cause detectable biologic change. (b) The pattern of biologic change, caused by that agent under similar conditions of exposure, actually exists in that person. (c) The pattern of biologic change is unique or sufficiently specific to distinguish it from patterns produced by other agents in the person's exposure history. (d) The pattern of biologic change associated with the particular agent in experimental conditions is in fact induced in the cells or body fluids of the particular individual, as demonstrated by in vitro experiments.

Professor Thilly's (Cariello and Thilly, 1986) pioneering use of gradient denaturing gels to determine the mutational spectra in human cells may offer a means of ascription that can surmount the existing multivariate obstacle:

> Based on the fact that mutagens induce specific patterns of gene mutations, (the methodology) allow(s) discrimination among mutagen-treated populations. The technique should allow direct screening of human tissue for genetic change, using human peripheral blood lymphocytes deficient in the enzyme hypoxanthine-guanine phosphoribosyl-transferase. The method is based on gradient denaturing gel electrophoresis, which separates short DNA molecules according to their melting properties. The melting behavior of DNA fragments is extremely sequence-dependent, and DNAs with single basepair substitutions often migrate differently. Even DNA fragments with the same basepair substitutions at different locations in the molecule have been resolved. Gradient denaturing gel electrophoresis has the

capacity to separate mutant DNA on the basis of the nature and position of the mutation.

Assuming that this or any other method of toxicologic "fingerprinting" gains acceptance through the peer review process, its reliability must still be established in tort litigation (*United States v. Williams*):

> A determination of reliability cannot rest solely on a process of "counting (scientific) noses." *** Selection of the "relevant scientific community" appears to influence the result. *** (U)nanimity of opinion in the scientific community, on virtually any scientific question, is extremely rare. Only slightly less rare is a strong majority. Doubtless, a technique unable to garner any support, or only minuscule support, within the scientific community would be found unreliable by a court. In testing for admissibility of a particular type of scientific evidence, whatever the scientific "voting" pattern may be, the courts cannot in any event surrender to scientists the responsibility for determining the reliability of that evidence. *** One indicator of evidential reliability is the potential rate of error. *** Another reliability indicia is the existence and maintenance of standards (such as a requirement of a minimum number of matches before a positive identification can be made). *** A third reliability factor can be the care and concern with which a scientific technique has been employed, and whether it appears to lend itself to abuse. *** A further indication of the reliability of the (scientific test) is its analogous relationship with other types of scientific techniques, and their results, routinely admitted into evidence. *** Lastly, a convincing element in determining reliability is the presence of "fail-safe" characteristics.

A recent exchange in the *Journal of the American Medical Association* demonstrates how swiftly the reliability of scientific tests involving biologic markers can be placed in issue. In an April 18, 1986, article (Hoffman, 1986) entitled, "Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin," the abstract states:

> In 1971, sludge wastes contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin were mixed with waste oil and sprayed on a dirt road at the Quail Run Mobile Home Park in Gray Summit, Mo. We performed a comprehensive examination of 154 exposed and 155 unexposed persons in the area. There were no consistent differences between the two groups on medical history, physical examination, serum and urinary chemistry studies, and neurologic tests. Results of liver function tests suggested possible subclinical effects. The exposed group had an increased frequency of anergy (11.8% versus 1.1%) and relative anergy (35.3% versus 11.8%). The exposed group also had nonstatistically significant increased frequencies of abnormal T-cell subset test results (10.4% versus 6.8%), a T4/T8 ratio of less than 1.0 (8.1 versus 6.4%) and an abnormality in the functional T-cell test results (12.6% versus 8.5%). These findings suggest that long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin is associated with depressed cell-mediated immunity, although the effects have not resulted in an excess of clinical illness in the exposed group. Further studies are indicated to elucidate the pathophysiology and clinical significance of these immunologic findings.

A lawyer, writing in the October 1986 edition of *Trial* magazine (Roisman, 1986), relied upon this study to support his assertion that:

> One important body system that is highly vulnerable to injury from exposure to toxic substances is the immune system. Relatively inexpensive and standard tests can disclose whether this system has been damaged. These tests are not new but have only recently been applied to establish causation in toxic tort cases.

The September 19, 1986 edition of the *Journal of the American Medical Association* contained a letter (Allison and Lewis, 1986) entitled, "Lack of health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin," which criticized the April 18th article, unknowingly invoking each reliability standard set forth in the legal opinion cited above. The letter noted that "(s)kin tests for delayed-type hypersensitivity are notoriously subject to reader bias, especially in the hands of inexperienced readers, such as those used in (the) study." The letter stated that the exposed subjects' responses to tests which "provide more objective information about cell-mediated immune status" were normal. The letter also observed that the "(f)ailure to generate cytotoxicity for allogeneic cells in vitro is reported to be the most sensitive indicator of TCDD exposure in experimental animals." Yet, "(t)here was no sign of any such failure, or of any other consistent defect in T-cell performance, in the group of persons exposed to TCDD." The letter concluded by reporting that the American Medical Association Council on Scientific Affairs and its Advisory Panel on Toxic Substances reviewed the most extensive experiences with the adverse effects of TCDD in humans and concluded that neither immune responses nor susceptibility to infectious diseases was altered.

The foregoing dialogue is not an atypical summary of the complex polemic courts must endure when evaluating the reliability of scientific tests. Even a general acceptance of a given test as reliable predictably results in collateral attacks relating to the manner in which the test is administered or corresponds with other tests in a particular case.

Understandably, few judges' scientific training is so eclectic as to prepare them to discern which experts' opinions merit adoption, nor do congested caseloads permit judges' independent study of genetic toxicology, organic chemistry, radiobiology or a myriad of other material disciplines. The disparity in expert witnesses' testimony is frequently beyond reconciliation. One federal district court judge (*Johnston v. United States*), discussing the conflicting expertise regarding radiation dose, referred to the disparity as "a huge, unbridgeable gap." Efforts to simplify matters by developing devices, such as probability of causation tables, spawn still additional technical issues. Moreover, even where such devices are employed, courts must still make findings regarding the input data, such as dose, dose rate and diagnosis, upon which such devices depend.

In summary, the use of biologic markers is hardly a requiem for toxic tort litigation—it may well engender more. If its evidentiary reliability can be demonstrated, its usefulness will be that judicial decisions regarding disease causation can be made with scientific certainty and without subjunctive reference to the defendant's purported negligence.

REFERENCES

Allen v. United States, 588 F. Supp. 247 (D. Utah 1984), *rev'd*, 816 F.2d 1417, 1421 (10th Cir. 1987), *petition for cert. filed* July 20, 1987.

ALLISON, A. and LEWIS, R. (1986). Lack of health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J. Amer. Med. Assoc.* **256** 1447.

AMERICAN LAW INSTITUTE (1965). *Restatement (Second) of Torts* §433.

CARIELLO, N. and THILLY, W. (1986). Use of gradient denaturing gels to determine mutational spectrum in human cells. *Basic Life Sci.* **38** 439.

HOFFMAN, R. (1986). Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J. Amer. Med. Assoc.* **255** 2031.

Johnston v. United States, 597 F. Supp. 374, 390 (D. Kan. 1984).

NATIONAL INSTITUTES OF HEALTH (1985). Report of the National Institutes of Health ad hoc working group to develop radioepidemiological tables.

NATIONAL RESEARCH COUNCIL (OVERSIGHT COMMITTEE ON RADIOEPIDEMIOLOGIC TABLES) (1984). Assigned share for radiation as a cause of cancer—Review of radioepidemiologic tables assigning probabilities of causation 35–36.

ROISMAN, A. (1986). Proving cause in toxic-tort litigation. *Trial* **22** 59.

THILLY, W. (1986). Personal communication.

United States v. Williams, 583 F.2d 1194 (2nd Cir. 1978).