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TOXICOGENOMICS: THE PROMISE OF CERTAINTY IN SCIENCE

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Environmental lawyers are often frustrated by the disconnect between science and law. In toxic tort cases, for example, a plaintiff must prove that her alleged exposure more likely than not caused her illness. This proof typically involves the aid of expert testimony from an epidemiologist. Most epidemiologists, however, do not speak the legal jargon of causation, but rather ask whether there is an "association" between a particular disease and exposure to a particular substance (or group of substances). Compounding the disconnect, epidemiologists disagree on when an "association" can be deemed "causative" in the tort context.

The legal/scientific disconnect is also encountered in the regulatory context when, for example, governmental agencies establish new exposure guidelines. Here outcome determinative policy choices will oftentimes trump sound scientific data by assuming the maximum amount of illness with the minimum amount of exposure.

A relatively new and rapidly maturing scientific sub-discipline called "toxicogenomics" (which some would subdivide into "toxicogenetics" and "toxicogenomics" – See Gary Marchant's article below) promises to give lawyers far more certainty with respect to medical causation issues, by providing greater precision for some biological pathways involved in proving medical causation. But will this tool be used correctly to clarify causation, or misused to support junk genomics? As with any new scientific field, use and misuse will operate in tandem.

What is Toxicogenomics?

Toxicogenomics combines toxicology (the study of toxins effects upon living organisms) with the scientific field of human genomics, which gives experts the ability to probe the human genome for particular causation pathways or genetic susceptibilities.

The now historic and highly publicized race to map the human genome resulted in the publication of the complete human genome map and sequence in 2001. From this we have learned that the structure of the human genome points scientists toward sequence variations in genes that respond to chemicals, pharmaceuticals, dietary supplements and other environmental agents.

How Do Scientists Test for Genetic Susceptibilities?

Human beings all share a common genetic blueprint. Indeed, 99 percent of human DNA sequences are the same. Because of these similarities, scientists have been able to develop two related techniques that allow thousands of genes to be analyzed at one time. These techniques are referred to as "microarrays" or "DNA chips." Microarrays and DNA chips contain thousands of known DNA sequences that will bind to complimentary strands of DNA. DNA chip technology allows for the culturing of cells (cells contain DNA) in both the presence and absence of a substance, such as chemicals, pharmaceuticals or cosmetics, to determine whether genes are activated or deactivated by such exposure. The activation or deactivation of a gene is what scientists refer to as "gene expression."

When genes are activated they produce a nucleic acid called messenger RNA (mRNA) that acts as a template for the production of a particular protein. Microarrays and DNA chips are capable of measuring the amount of mRNA expressed before and after exposure to a substance. These changes in gene activity are precursors of other more visible symptoms of harm that become tumors. Gene tests may

detect harm at lower doses than those used in current animal testing models.

Although human DNA sequences are remarkably similar across the board, scientists believe that variations in the genetic blueprint, known as DNA sequence variations, are the key to understanding why a toxic substance might cause cancer in one individual but not in another. Single nucleotide polymorphisms (SNPs or snips for those hoping to sound tech savvy) are DNA sequence variations (polymorphisms) that occur in nucleotides (the smallest building blocks of DNA). Scientists believe that SNPs precertain diseases and may influence their response to chemicals, drugs and other substances.

How Will Toxicogenomics Impact My Practice?

Toxicogenomics will have an impact on regulatory, toxic tort, public health and chemical safety issues. In December 2000, the National Institute of Environmental Health Sciences (NIEHS) established the National Center for Toxicogenomics (NCT). (See www.niehs.nih.gov). The NCT coordinates research in toxicogenomics, using a database containing comprehensive toxicological gene expression data that can be used for predictive toxicology.

Research conducted at the NCT will aid governmental agencies in establishing new regulatory guidelines, such as limitations on air emissions, wastewater discharges, cleanup standards of contaminated sites, worker exposure and children's health initiatives. In theory, toxicogenomics should support better, more precise regulatory standards. This information will also be used in toxic tort lawsuits. In theory, toxicogenomics should support better science in assessing causation between exposure and disease, and not necessarily favor plaintiffs or defendants.

NIEHS recently announced that it is launching a pilot study with 600 patients at several University of North Carolina outpatient clinics, using blood drawn for other medical purposes to isolate DNA and screen for "environmentally sensitive" SNPs. Tom Hawkins, NIEHS Press Release, *NIEHS and UNC to Collaborate on Registry of 20,000 Subjects to Relate Gene Variants and Environmental Disease*, (Jan. 14, 2004) http://www.niehs.nih.gov/oc/news/polyreg.htm.

The pilot study is unusual in that patient identifiers will be maintained in coded form, giving scientists the ability to re-contact participants at a later date for follow-up studies. Follow-up studies will allow scientists to identify groups of individuals with SNPs in "environmentally sensitive" genes, linking genetic variants with health effects. Scientists believe that this "pioneering initiative" will increase understanding of how genes interact with the environment, including the body's response to medicines. In the process, they could well carve a trail through the human genome that litigants could possibly follow in future litigation.

What Have We Learned So Far?

Scientists do not yet fully understand how to interpret the significance of activating a gene or which SNPs could indicate genetic susceptibility. Many factors influence whether a gene will be activated, including dose and duration of exposure. Given a minimal understanding of the relationship between gene expression and doses inducing toxicity, gene expression data is premature in hazard identification or risk assessments. Basic questions of relevance still need to be addressed. For example, how many and which genes should be measured to characterize a toxic response, and how will scientists distinguish such a response from physiologically adaptive responses that are not linked to toxicity? Many questions

regarding the reliability of toxicogenomics must be addressed by the scientific community.

What Does the Future Hold?

The future promises a new era in which science may be moving faster than the law. In the next few years, toxicogenomics will show how chemicals and other environmental agents perturb biological systems. Unfortunately, in the short run, we may see toxicogenomic data interpreted incorrectly to establish unsound or "junk" regulatory policy or to expand private liability.
In the long run, however, toxicogenomics could force regulators and plaintiffs' lawyers to confirm findings of harm at the genomic level. Substances that do not activate genes necessary to induce a particular toxic endpoint could then be exonerated. Courts may in the future opt to reject expert causation opinion where toxicogenomic analysis is lacking or contradictory to the proposition asserted. Finally, a better understanding of the dose-response relationship using genetics may finally put to rest concerns about extremely low dose exposures, and may result in substantial improvements in the establishment of safe levels of contaminants in air, water and food. Environmental and toxic tort attorneys who understand this emerging area of inquiry will be better able to serve the interests of their clients.

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