Toxicogenomics: Toward the Future of Toxic Tort Causation

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I. Introduction

Plaintiff suspects that a chemical in her city's water supply has caused her to develop a rare form of liver cancer. Defendant, a company in Plaintiff's city, has been discharging the chemical into the water for a number of years. Both parties in the toxic tort litigation are at the mercy of an unevenly developed and often-insufficient body of science to establish or rebut the required causation element.

This article will examine the current causation paradigm in toxic tort litigation, pointing out its specific weaknesses. The article will then introduce an emerging discipline, toxicogenomics, which will eventually make it possible to specifically describe the molecular pathways leading from exposure to injury, and in so doing will greatly improve the reliability of causation evidence in toxic tort cases to the benefit of both plaintiffs and defendants. To illustrate its potential usefulness, this article will walk through a hypothetical toxicogenomics experiment involving a suspected liver toxin. The article will conclude by suggesting that judges controlled by *Daubert v. Merrell Dow Pharmaceuticals, Inc.*[2] would be wise not to admit such evidence until more research can definitively link the described molecular pathways to the specific injury.

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[2] 509 U.S. 579 (1993).

II. Current Causation Paradigm in Toxic Tort Litigation

It is a fundamental premise of tort law that a plaintiff must establish that the defendant's acts or omissions proximately caused her injury in order to prevail.[3] Historically, a variety of inexact tools have been used to attempt to establish a causal link between a substance and an adverse effect.[4] A plaintiff in toxic tort litigation must prove, by a preponderance of the evidence, both that the substance at issue *could* cause the general type of injury suffered (general causation) and that it *did* cause her injury (specific or individual causation).[5] Clearing both of these evidentiary hurdles currently is a significant challenge. It is often so daunting that some plaintiffs opt instead to pursue novel causes of action.[6] If validated by the scientific community, toxicogenomics could become an important tool for plaintiffs and defendants alike.

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[3] *See*, *e.g.*, James Pizzirusso, *Increased Risk, Fear of Disease and Medical Monitoring: Are Novel Damage Claims Enough to Overcome Causation Difficulties in Toxic Torts?*, 7 ENVTL. LAW. 183, 186 (2000).

[4] Mark Geistfeld, *Scientific Uncertainty and Causation in Tort Law*, 54 VAND. L. REV. 1011, 1012 (2001). The traditionally available tools generally have involved observing "health outcomes in populations of animals exposed to large amounts of the substance, study[ing] the biochemical effects of the substance on cells, organs, and embryos, [or] compar[ing] the substance's chemical composition to other known health hazards." *Id.*

[5] Carl F. Cranor & David A. Eastmond, *Article: Scientific Ignorance and Reliable Patterns of Evidence in Toxic Tort Causation: Is There a Need for Liability Reform*, 64 LAW & CONTEMP. PROB. 5, 15 (2001); *see also* Joseph Sanders & Julie Machal-Fulks, *Article: The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, 64 LAW & CONTEMP. PROB. 107, 110 (2001); Andrew See, *Use of Human Epidemiology Studies in Proving Causation*, 67 DEF. COUNS. J. 478, 479 (2000).

[6] Pizzirusso, *supra* note 3 (describing the history, policies, and specific examples of novel causes of action such as "fear of" a disease, "increased risk" of a disease, and "medical monitoring"); *cf.* Norfolk & Western Railway Co., v. Freeman Ayers, 538 U.S. 135 (2003) (recognizing that a defendant who has already been found liable to a plaintiff for causing her asbestosis (asbestosis causation established), may also be liable to that same defendant for emotional distress damages based on a reasonable and genuine fear of eventually developing cancer (cancer causation not established)).

A. General Causation

To prove general causation, plaintiffs often proffer epidemiological evidence. Indeed, some cases have even required epidemiology studies to satisfy the general causation burden.[7] In any epidemiology study, "subsets or samples of populations" are examined "to determine whether there is an association between exposure to a substance or factor and subsequent disease or injury."[8] In general, "large-scale" epidemiology studies can be probative as to whether a chemical or other potentially toxic substance can cause an injury since they involve either "comparing the incidence of adverse health outcomes in groups of exposed and non-exposed individuals, or comparing the incidence of exposure across injured and healthy groups."[9]

Unfortunately, epidemiology studies "are expensive, time-consuming, and require that a large number of people be exposed to the substance."[10] Given the current capabilities and limitations of science, however, "the hazardous properties of [many] substance[s] often cannot be established" via any other mechanism.[11] Simply put, the existence of epidemiology studies may be the only avenue to meet the general causation burden in a toxic tort case. Furthermore, unless and until a party establishes general causation, any evidence regarding specific or individual causation likely would be deemed irrelevant and inadmissible.[12]

B. Specific Causation

Another major limitation of epidemiology studies is that they "are relevant only to general causation" since results from such studies cannot establish whether a particular exposure or series of exposures actually caused the disease or injury in a

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[7] See, *supra* note 5, at 479. However, epidemiological studies may not be necessary if a "causal mechanism for the disease" is known. *Id.*
[8] *Id.* at 478.
[9] Geistfeld, *supra* note 4, at 1012.
[10] *Id.*; *see also* Chrisitiana P. Callahan, *Molecular Epidemiology: Future Proof of Toxic Tort Causation*, 8 ENVTL. LAW. 147, 162 (2001).
[11] Geistfeld, *supra* note 4, at 1012.
[12] See, *supra* note 5, at 478.

specific individual.[13] Determining specific causation often is much more difficult than establishing general causation.[14] Additionally, the complex etiology of many diseases creates the possibility that any of a variety of factors could have caused the plaintiff's injury.[15]

To sort through the myriad possible causes of injury, courts often rely on a physician performing a differential diagnosis[16] where the physician, as an expert witness, considers and rules out potential causes of injury, finally stating an opinion as to whether the particular substance at issue caused the plaintiff's injury.[17] Despite advances in medical science, there still are significant limitations to differential diagnoses[18] and some commentators believe that the admissibility of such evidence has become even more difficult in the wake of *Daubert*.[19] Given the current

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[13] *Id.*

[14] Callahan, *supra* note 10, at 163; Sanders & Machal-Falks, *supra* note 5, at 137 (stating that proving specific causation in toxic tort litigation is "one of the more difficult causal issues in torts today").

[15] Callahan, *supra* note 10, at 163.

[16] *See id.*; Sanders & Machal-Falks *supra* note 5, at 120 (noting that "whenever there are competing causes for the plaintiff's injury, an expert must attempt a differential diagnosis before his testimony will be admitted" and that "[c]ourts accept the general validity of the technique of differential diagnosis"); Gary Sloboda, *Article: Differential Diagnosis or Distortion?*, 35 U.S.F.L. REV. 301, 303 (2001) (describing differential diagnoses as "'patient-specific process[es] of elimination' used to identify the cause of a medical problem by eliminating possible causes until the most probable cause is isolated").

[17] Callahan, *supra* note 10, at 163; Sanders & Machal-Fulks, *supra* note 5, at 107.

[18] Sloboda, *supra* note 16, at 304 ("Although medical and scientific knowledge has advanced significantly in the twentieth century, making medical diagnosis more precise, the process of differential diagnosis remains 'a mixture of science and art, far too complicated for its accuracy to be assessed quantitatively or for a meaningful rate of error to be calculated.'").

[19] Sanders & Machal-Fulks, *supra* note 5, at 137.

> We believe that it is fair to say that differential diagnosis testimony generally is looked upon with greater skepticism than was the case prior to the Daubert revolution. Courts are less likely to admit the testimony. In part, this is because in the toxic tort arena plaintiffs are attempting more difficult causal arguments. We believe it is also because courts have

limitations regarding both general and specific causation, toxic tort litigants need a tool that can eliminate much of the guesswork by definitively linking a substance to the injury that it causes.

III. Toxicogenomics

Toxicogenomics is a relatively new science.[20] Once fully developed, the discipline should greatly improve the current causation paradigm. A multidisciplinary[21] field focused on understanding the role of genes in responding to toxicants and other stressors,[22] toxicogenomics will eventually advance toxicology beyond its current "gross endpoints."[23]

Fundamental to toxicogenomics is the hypothesis that, following toxicant exposure and preceding any currently measurable adverse effect, gene expression is modulated in a specific and measurable way.[24] Once described, these patterns and

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become more demanding by requiring better science before admitting testimony.

Id.

[20] Tina Adler, *The New Biology*, 111:1T ENVTL. HEALTH PERSP.: TOXICOGENOMICS A14 (2003) (dating the field to "about 1996, when rapid genetic sequencing first became possible").

[21] Gary E. Marchant, *Toxicogenomics and Toxic Torts*, 20(8) TRENDS BIOTECHNOLOGY 329 (2002); Kenneth S. Ramos, *EHP Toxicogenomics: A Publication Forum in the Postgenome Era*, 111:1T ENVTL. HEALTH PERSP.: TOXICOGENOMICS A13 (2003) ("'Toxicogenomics' describes an emerging discipline that combines expertise in toxicology, genetics, molecular biology, and environmental health to elucidate the response of living organisms to stressful environments.").

[22] Erin E. Dooley, *txgnet: EHP Toxicogenomics*, 111:1T ENVTL. HEALTH PERSP.: TOXICOGENOMICS A15 (2003).

[23] Hisham K. Hamadeh et al., *Discovery in Toxicology: Mediation by Gene Expression Array Technology*, 15(5) J. BIOCHEMISTRY MOLECULAR TOXICOLOGY 231, 231 (2001) (noting "body and organ weight changes and histopathological observations" as examples of such endpoints); *see also* Geistfeld, *supra* note 4.

[24] Michael Waters et al., *Systems Toxicology and the Chemical Effects in Biological Systems (CEBS) Knowledge Base*, 111:1T ENVTL. HEALTH PERSP.: TOXICOGENOMICS 15, 15 (2003).

sequences of gene expressions will constitute response "signatures" unique to specific toxicants or classes of toxicants.[25]

Two recent studies strongly support this hypothesis.[26] In one, conducted by Zeytun et al., scientists administered a known toxicant, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), to mice and then monitored eighty-three genes for a period following the exposure.[27] A "significant proportion" of the genes examined showed some form of altered expression following exposure.[28] By studying these patterns of altered expression, researchers may be able to identify "'finger print' genes, which could serve as biomarkers for predicting toxicity induced by a specific class of toxicants."[29] In an even more convincing study by Hamadeh, et al., researchers treated rats with several different chemicals and monitored a number of genes following the exposures.[30] The researchers successfully developed distinct gene expression profiles for each of the classes of chemicals tested, even though some of those chemicals had the exact same previously measurable exposure endpoint.[31] These two studies strongly support the hypothesis that following exposure to a specific toxic substance, gene modulation will occur in a manner that is both measurable and predictable.

The initial toxicogenomics studies suggest that the field holds great promise for toxic tort litigants. Eventually, it could reduce or eliminate much of the current causation guesswork by

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[25] *Id.*

[26] Ahmet Zeytun et al., *Analysis of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin-Induced Gene Expression Profile in Vivo Using Pathway-Specific cDNA Arrays*, 178 TOXICOLOGY 241 (2002); Hisham K. Hamadeh et al., *Gene Expression Analysis Reveals Chemical-Specific Profiles*, 67 TOXICOLOGICAL SCI. 219 (2002).

[27] Zeytun et al., *supra* note 26, at 247.

[28] *Id.*

[29] *Id.* (noting, however, this study "failed to discriminate between toxicant classes based on gene expression profiles"). According to the researchers, this failure was based on the inclusion of genes that were too sensitive to minor variations, and the suggestion was made for future researchers to find and use only those genes that "are altered in a consistent and reproducible fashion." *Id.* at 256.

[30] Hamadeh et al., *supra* note 26, at 225.

[31] *Id.*

generating evidence that describes how a toxic substance would affect a person at the molecular level.[32] As previously stated, the promise of toxicogenomics extends to all parties involved in toxic tort litigation. Commentators,[33] defense groups,[34] and plaintiffs' groups[35] alike have already recognized its potential importance.

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[32] *Id.*

[33] *See* Geistfeld, *supra* note 4, at 1032 n.54 ("[T]oxicogenomics involves the laboratory testing of animals or cells to determine the pattern of gene activity involved upon exposure to a potentially hazardous substance. 'This pattern of gene activity, at least in theory, should indicate whether the chemical is toxic, much as DNA fingerprints are used to judge the guilt or innocence of criminal suspects.'"); Gary E. Marchant, *Genetics in the Courtroom: Genetics and Toxic Torts*, 31 SETON HALL L. REV. 949, 980 (2001) ("The rapidly growing database of toxicological information from toxicogenomics should assist tort litigants in identifying toxic agents and proving the presence or absence of causation."); Susan R. Poulter, *Genetic Testing in Toxic Injury Litigation: The Path to Scientific Certainty or Blind Alley?*, 41 JURIMETRICS J. 211, 211 (2001) ("Rapid increases in the ability to identify disease genes and disease susceptibility genes and the expanding field of toxicogenomics suggest that genetic testing could become an important part of causal proof in toxic injury litigation."); *see* Gary E. Marchant, *Genetic Susceptibility and Biomarkers in Toxic Injury Litigation*, 41 JURIMETRICS J. 67, 75 (2000) ("These new techniques will result in more rapid screens for toxicity, which is critical given the thousands of commercial substances for which inadequate toxicity data are available. In addition to identifying toxic compounds, these techniques will also greatly expand the understanding of the mechanism of toxicity for many substances, resulting in more realistic risk estimates. This influx of new toxicological data will undoubtedly benefit future toxic tort litigants.").

[34] Todd M. Hooker, *The Brave New World of Toxicogenomics*, 16 (11) ENVTL. COMPLIANCE LITIG. STRATEGIST (April 2001), *available at* http://www.lowenstein.com/new/thebraveworld_April2001.pdf (on file with the North Carolina Journal of Law & Technology) ("In the long run, toxicogenomics has the potential to impose the burden on regulators and plaintiffs' lawyers to prove their positions with documented, confirmed findings at the human genome level. Substances that do not activate genes whose activation is necessary (albeit rarely sufficient) to induce a particular toxic endpoint may be exonerated.").

[35] Pat Phibbs, *Genomics Will Bring Changes*, SOC'Y ENVTL. JOURNALISTS NEWSL. (Soc'y Envtl. Journalists), at 12–13, Winter 2001, *available at* http://www.sej.org (on file with the North Carolina Journal of Law & Technology) ("The [toxicogenomics] field is expected to have a profound impact on scientists' understanding of toxicity and illness, public health, toxic tort litigation, the use of animals in toxicity research, environmental and

A. The Scientific Underpinnings of Toxicogenomics

In a relatively short period, scientists have made a remarkable amount of progress toward discovering and describing our molecular makeup.[36] From "[t]he rediscovery of Mendel's laws of heredity" early in the twentieth century, to the elucidation of the DNA double helix fifty years ago, and the sequencing and analysis of individual strands of DNA today, humans have expanded exponentially the frontiers of genetics over the past hundred years.[37] Two particular advances in the field promoted the emergence of toxicogenomics as a discipline.[38] First, the rapid development of DNA sequencing capabilities over the past two decades has allowed scientists to sequence entire genomes. Second, researchers are utilizing the vast information contained in these genome sequences via sophisticated DNA microarrays.

1. Gene Sequencing

One of science's most recent endeavors, and one that still is very much ongoing, is the development of methodologies and equipment for rapidly sequencing an organism's DNA. Sequencing a strand of DNA is a multi-step[39] process resulting in a

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occupational regulations, worker's rights, and, perhaps ecological management.").

[36] INTERNATIONAL HUMAN GENOME SEQUENCING CONSORTIUM, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (2001) [hereinafter Consortium].

[37] *Id*.

[38] NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, MICROARRAYS: CHIPPING AWAY AT THE MYSTERIES OF SCIENCE AND MEDICINE, *at* http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html (last visited Oct. 14, 2003) (on file with the North Carolina Journal of Law & Technology).

[39] OAK RIDGE NATIONAL LABORATORY, HUMAN GENOME PROJECT INFORMATION: FACTS ABOUT GENOME SEQUENCING, *at* http://www.ornl.gov/hgmis/faq/seqfacts.html (last visited Oct. 16, 2003) (on file with the North Carolina Journal of Law & Technology).

> Chromosomes must first be broken into much shorter pieces . . . . . Each short piece is used as a template to generate a set of fragments that differ in length from each other by a single base that will be identified in a later step . . . . The fragments in a

comprehensive description of the organism's individual base sequence.[40] The sequence of bases in DNA is the most definitive means of distinguishing among species and among individuals within a species.[41]

DNA sequencing is currently complete for hundreds of viruses, viroids, plasmids, and organelles, as well as for dozens of other simple organisms.[42] In 1995, researchers completed the first

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> set are separated by gel electrophoresis . . . . New fluorescent dyes allow separation of all four fragments in a single lane on the gel . . . . The final base at the end of each fragment is identified . . . recreat[ing] the original sequence of As, Ts, Cs, and Gs for each short piece generated in the first step. Automated sequencers analyze the resulting electropherograms, and the output is a four-color chromatogram showing peaks that represent each of the four DNA bases. . . . [C]omputers are used to assemble the short sequences . . . into long continuous stretches that are analyzed for errors, gene-coding regions, and other characteristics.

Id.

[40] *Id.*

[41] NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, WHAT IS A GENOME?, *at* http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html (last visited Oct. 14, 2003) (on file with the North Carolina Journal of Law & Technology).

> A DNA chain is made up of four chemical bases: adenine (A) and guanine (G), which are called purines, and cytosine (C) and thymine (T), referred to as pyrimidines. Each base has a slightly different composition, or combination of oxygen, carbon, nitrogen, and hydrogen. In a DNA chain, every base is attached to a sugar molecule (deoxyribose) and a phosphate molecule, resulting in a nucleic acid or nucleotide. Individual nucleotides are linked through the phosphate group and it is the precise order, or sequence, of nucleotides that determines the product made from that gene.

Id.

[42] *See* CONSORTIUM, *supra* note 36. A large amount of sequencing information has been made available via public distribution on the Internet. "GenBank is the NIH genetic sequence database, an annotated collection of all publicly available DNA sequences" both human and otherwise, and as of February 7, 2003, it contained 28.5 billion base pairs in 22.3 million sequences. GENBANK, GROWTH OF GENBANK, *at* http://www.ncbi.nih.gov/Genbank/genbankstats.html (last visited Oct. 14, 2003) (on file with the North Carolina Journal of Law & Technology).

DNA sequence of a free-living organism and the sequencing of a number of other more complex organisms rapidly followed.[43]

The most ambitious DNA sequencing project by far is the collaborative[44] effort to map the human genome.[45] Scientists published a draft version of the human genome sequence in February 2001,[46] and announced that this enormous effort was finished on April 14, 2003.[47] The National Center for Biotechnology Information currently places the number of known human genes at about 24,000 not including the genes on the sex chromosomes.[48]

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[43] Emile F. Nuwaysir et al., *Microarrays and Toxicology: The Advent of Toxicogenomics*, 24 MOLECULAR CARCINOGENESIS 153, 153–59 (1999).

[44] *See* CONSORTIUM, *supra* note 36 (noting that the task has involved a collaborative effort among twenty labs worldwide).

[45] *Id.*

> The sequence of the human genome is of interest in several respects. It is the largest genome to be extensively sequenced so far, being 25 times as large as any previously sequenced genome and eight times as large as the sum of all such genomes. It is the first vertebrate genome to be extensively sequenced. And, uniquely, it is the genome of our own species.

Id.

[46] Hooker, *supra* note 34. The race to the finish for the sequencing of the human genome project had an ample amount of drama involved. Two labs ultimately published simultaneously in separate journals. Celera Genomics, a biotechnology laboratory in Rockville, Maryland published the sequenced human genome in SCIENCE and the government-sponsored Human Genome Project published in NATURE.

[47] NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, GENOME SEQUENCING, *at* http://www.ncbi.nlm.nih.gov/genome/seq/ (last visited Oct. 14, 2003) (on file with the North Carolina Journal of Law & Technology) [hereinafter GENOME SEQUENCING].

[48] NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, HUMAN GENOME RESOURCES, *at* http://www.ncbi.nlm.nih.gov/genome/guide/human (last visited Oct. 17, 2003) (on file with the North Carolina Journal of Law & Technology).

2. Microarrays

Given the vast size of a DNA molecule[49] and the potential amount of information available therein, a research tool capable of exploiting such large quantities of information is necessary. Microarrays are such a tool.[50] A microarray is typically either a glass slide or a computer chip that has had a specific arrangement of known gene sequences either spotted onto it or engineered onto it, respectively.[51]

Although the origins of microarrays can be traced to the mid to late 1980s,[52] today's microarray is highly evolved and capable of vastly superior analytical feats. As one researcher noted, while "[t]he simultaneous examination of a hundred genes is descriptive; the simultaneous examination by comparison and clustering of tens of thousands of genes is a new way to do science."[53] Another researcher explained, "the microarray approach, which allows the monitoring of expression levels of thousands of genes simultaneously, is a tool of unprecedented power for use in toxicology studies."[54]

Microarrays typically come in two varieties: "oligonucleotide-based arrays and [complementary DNA or] cDNA arrays."[55] Given the increasing commercial availability of microarrays[56] and enhanced capacity to simultaneously monitor

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[49] *See* GENOME SEQUENCING, *supra* note 47; *see also* Press Release, NATIONAL HUMAN GENOME RESEARCH INSTITUTE, INTERNATIONAL CONSORTIUM COMPLETES HUMAN GENOME PROJECT (Apr. 14, 2003) (noting that human DNA is comprised of three billion base pairs) *at* http://www.genome.gov/11006929 (on file with the North Carolina Journal of Law & Technology).

[50] Charles W. Schmidt, *Toxicogenomics*, 111:1T ENVTL. HEALTH PERSP.: TOXICOGENOMICS A20, A22 (2003).

[51] Philip M. Iannaccone, *Toxicogenomics: "The Call of the Wild Chip,"* 109(1) ENVTL. HEALTH PERSP. (editorial) (2001).

[52] Roger Ekins & Frederick W. Chu, *Microarrays: Their Origins and Applications*, 17(6) Trends in Biotechnology 217 (1999); *see also* Adler, *supra* note 20.

[53] *See* Iannaccone, *supra* note 51.

[54] Nuwaysir, *supra* note 43, at 153.

[55] *Id.*; *see also* Hamadeh, *supra* note 23, at 231.

[56] William D. Pennie et al., *The Principles and Practice of Toxicogenomics: Applications and Opportunities*, 54 TOXICOLOGICAL SCI. 277, 277 (2000)

very large numbers of genes, most of the current toxicogenomics research utilizes cDNA microarrays.

B. An Example of Microarray Application in Toxicogenomics

Experimentation with cDNA microarrays involves three broad steps: design of the microarray, application of the microarray, and analysis of data. For purposes of explanation, this article will examine a simplistic hypothetical scenario. Assume that a researcher working at a cereal company has developed a new food additive, but he is concerned that it might adversely affect the liver. For simplicity in this hypothetical, assume also that this researcher was only concerned with discovering whether one particular gene ("Target Gene") would be expressed in liver tissue following exposure to this suspected hepatotoxin.[57]

1. Slide Design

The first step in the process, microarray design, is quickly becoming a major industry.[58] A necessary pre-design step involves researching whether anyone holds a patent on the Target Gene, and then attempting to obtain licensing agreements if necessary. At least some of the companies developing microarrays for

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(noting that the manufacture of microarrays for specific purposes by "commercial vendors, pharmaceutical companies, and academic institutions" is becoming more and more common).

[57] NATIONAL LIBRARY OF MEDICINE, TOXICOLOGY GLOSSARY: H, *at* http://www.sis.nlm.nih.gov/ToxTutor/Tox1/glossh.htm (defining hepatotoxin as "[a] systemic poison whose target organ is the liver") (last visited Oct. 18, 2003) (on file with the North Carolina Journal of Law & Technology)

[58] Kristin Lewotsky, *Growing, Growing, Gone: The Biotechnology Market is Poised to Soar*, OE MAG., Feb. 2002, at 18-19, a*vailable at* http://oemagazine.com/fromTheMagazine/feb02/pdf/specialfocus.pdf (on file with the North Carolina Journal of Law & Technology). Microarrays are "a high-growth area, with applications in industries like biotechnology, food and beverage, and life science . . . ." *Id.* Growth estimates suggest that the market will grow "from $400 million in 2000 to $1 billion by 2005 . . . . The protein-chip market alone . . . will grow from the 2000 figure of $44 million to reach $490 million by 2006." *Id.*

commercial use resent this step[59] and have lobbied for legislation that would allow non-commercial researchers to use such sequences without first obtaining a license.[60] For purposes of this hypothetical, assume the Target Gene has not been patented.

To prepare the microarray slide, a researcher would collect, isolate, and reverse transcribe single-stranded mRNA coding for the Target Gene to produce cDNA.[61] The researcher then would degrade the mRNA from the newly formed mRNA-cDNA molecule, and the single-stranded cDNA molecule would serve as a template for the formation of a double-stranded DNA molecule.[62] Next, she would multiply via polymerase chain reaction ("PCR") the resultant DNA molecule and purify it.[63] Finally, the researcher would denature the double-stranded DNA so that many single strands of DNA could be "spotted" onto the slide.[64] In the end, exactly half of the single stranded DNA molecules on the slide

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[59] "'There should be no patenting of gene sequences, period. They were invented by nature,' said Barbara Caulfield, general counsel for [Affymetrix]. 'This a position Affymetrix feels strongly about.'" Tom Abate, *Do Gene Patents Wrap Research in Red Tape?*, SAN FRANCISCO CHRON., Mar. 25, 2002, *available at* http://www.sfgate.com/cgi-bin/article.cgi?f=c/a/2002/03/25/BU97425.DTL (on file with the North Carolina Journal of Law &Technology).

[60] Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967 §§ (j)(1), (2)(E), 107th Cong. (2002). The bill is very broad regarding who is considered a researcher. "It shall not be an act of infringement for *any* individual or entity to use *any* patent for or patented use of genetic sequence information for purposes of research." *Id.* (emphasis added). "[T]he term 'research' means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." *Id.*

[61] NATIONAL HUMAN GENOME RESEARCH INSTITUTE, MICROARRAY PROJECT, *at* http://research.nhgri.nih.gov/microarray/Protocols.pdf (last visited Oct. 1, 2003) (on file with the North Carolina Journal of Law & Technology) [hereinafter NHGRI].

[62] NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, ESTS: GENE DISCOVERY MADE EASIER, *at* http://www.ncbi.nlm.nih.gov/About/primer/est.html (last visited Oct. 14, 2003) (on file with the North Carolina Journal of Law & Technology) [hereinafter ESTs].

[63] NHGRI, *supra* note 61.

[64] *Id.*

would be complementary to cDNA produced via reverse transcription of the Target Gene mRNA.

The researcher would then coat the slide with poly-L-lysine, which would produce a "surface that is both hydrophobic and positively charged. The hydrophobic character of the surface minimizes spreading . . . and the charge" helps to position the single strands of DNA on the slide surface so that hybridization is enhanced.[65] The slide is designed such that when single-stranded cDNA coding for the Target Gene is applied, that cDNA strand will hybridize with the single-stranded DNA already on the slide. While this hypothetical is focusing on only a single Target Gene for illustration purposes, remember that the revolutionary impact of microarrays is their ability to simultaneously monitor tens of thousands of genes on a single slide via these same or similar techniques.[66]

2. Application of the Newly Designed Microarray in Target Gene Experimentation

Following preparation of the microarray, a researcher would harvest cells from both the unexposed liver tissue and the hepatotoxin-exposed liver tissue.[67] She would then isolate and purify the total RNA present in those cell samples.[68] Each of these total RNA mixtures would undergo reverse transcription to produce the cDNA molecules to be applied to the slide.[69] The researcher would differentially label the two sets of cDNA molecules during reverse transcription to distinguish between the unexposed and hepatotoxin-exposed samples.

Reverse transcription is a process whereby single-stranded mRNA is used as a template to produce single-stranded cDNA.

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[65] *Id.*
[66] *See supra* text accompanying notes 52–53.
[67] Emile F. Nuwaysir, Design, Generation, and Used of cDNA Microarrays on Glass, SOT2000: Continuing Education Course PM-16, Toxicogenomics in the Trenches (Mar. 19, 2000) (unpublished presentation materials), *available at* http://dir.niehs.nih.gov/microarray/figures/background.pdf (on file with the North Carolina Journal of Law & Technology).
[68] NHGRI, *supra* note 61.
[69] Nuwaysir, *supra* note 43.

Reverse transcription begins when a primer attaches to an mRNA molecule. To form the cDNA molecule, an enzyme, usually reverse transcriptase, responds to the primer and begins sequentially adding deoxynucleotide triphosphates (dNTPs) that are complementary to the bases on the mRNA strand. To ensure that the entire cDNA molecule is accurately produced, equal amounts of four dNTPs, typically dATP, dTTP, dCTP, and dGTP, would be present in the solution where the reverse transcription was occurring.[70] Thus, reverse transcription would occur in a solution consisting primarily of (1) the RNA templates, (2) the initiation primer, (3) reverse transcriptase, and (4) enough of each dNTP such that when reverse transcriptase, in extending the cDNA strand, seeks to add a particular dNTP that is complementary to the base on the mRNA strand, there are sufficient quantities of each dNTP present in the solution for it to be able to effectively do so.

To label these forming cDNA strands, the researcher would tag one of the four available dNTPs with a fluorescent dye[71] so that the dye would be incorporated into the cDNA molecule each time that particular dNTP was added by the reverse transcriptase.[72] To

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[70] OREGON HEALTH & SCIENCE UNIVERSITY DIVISION OF MEDICAL INFORMATICS AND OUTCOMES RESEARCH, REVERSE TRANSCRIPTION PROTOCOL, *at* http://medir.ohsu.edu/~geneview/protocol/Reverse%20Transcription%20 Protocol.pdf (last visited Oct. 17, 2003) (on file with the North Carolina Journal of Law & Technology); ESTs, *supra* note 62 (noting that the dNTPs generally used are dATP, dTTP, dCTP, and dGTP, where "A" represents adenine, "T" represents thymine, "C" represents cytosine, and "G" represents guanine). In the labeling step, however, a number of protocols utilize dUTP instead of dTTP, where "U" represents Uracil. Regardless, adenine is always complementary to thymine and uracil, and cytosine is always complementary to guanine. *Id.*

[71] *See*, *e.g.*, Hamadeh, *supra* note 23, at 232.

[72] Iannaccone, *supra* note 51. This is one of the most common methods of incorporating a fluor into the sequence that is then detectable post-transcription, but there are certainly a number of variations on this theme. For examples of other methods, *see* JOSEPH DERISI, AMINO-ALLYL DYE COUPLING PROTOCOL, *at* http://www.microarrays.org/pdfs/amino-allyl-protocol.pdf (June 2001) (describing a method of incorporating an amino-allyl during the transcription process which could then be labeled with a dye post-transcription) (on file with the North Carolina Journal of Law & Technology); Affymetrix, Array Manufacturing, *at* http://www.affymetrix.com/technology/ge_analysis/index.affx (last visited Oct.

differentiate between the two samples, each reverse transcription process would use the same dNTP, but would be tagged with a different fluorescent substance. For example, the RNA from the unexposed cells might undergo reverse transcription in the presence of Cy5-dCTP, which would fluoresce red when excited by one laser, and the RNA from the hepatotoxin-exposed cells might undergo reverse transcription in the presence of Cy3-dCTP, which would fluoresce green when excited by another laser.[73] In this scenario, each time the reverse transcriptase came to a guanine in the RNA strand, it would add a fluorescently tagged dCTP (cytosine is complementary to guanine) to the forming cDNA strand.

The researcher would then mix together the two sets of differentially tagged cDNA strands and apply them to the slide.[74] If the Target Gene were expressed in either of the two samples, the cDNA would hybridize with the single stranded DNA molecules already present on the slide.[75] The cDNA that did not hybridize would then be washed off the slide.[76] Different lasers would be used to excite the fluorescent tags within any hybridized strands, eliciting a range of fluorescent responses that could be detected and quantified in an automated reader.[77]

3. Analyzing the Data from the Microarrays

After analysis of the different fluorescent responses, the color variations would quantify if, and to what extent, the Target Gene was expressed in the tissues of the hepatotoxin-exposed and unexposed liver samples. Since the original hypothesis in this hypothetical was whether the Target Gene would be expressed following hepatotoxin exposure, these data would be sufficient to test that hypothesis. However, a researcher could not conclude,

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11, 2003) (diagramming use of biotin-labeled cRNA) (on file with the North Carolina Journal of Law & Technology).

[73] Hamadeh, *supra* note 23, at 232.

[74] Nuwaysir, *supra* note 67, slide 6.

[75] *Id.*

[76] NHGRI, *supra* note 61.

[77] Iannaccone, *supra* note 51.

based solely on the results of this experiment, that any measurable gene expression was an indicator of toxicity. Indeed, one of the major difficulties facing toxicogenomics is determining what, if anything, a particular gene expression or pattern of gene expressions indicates.[78]

i. Phenotypic Anchoring

To improve the utility of toxicogenomics data in general, and to make it valuable to litigants in toxic tort cases, it is essential to tie gene expression patterns to standard toxicology indices.[79] Phenotypic anchoring refers to the correlation of the gene expression profile data with well-established toxicity data such as "toxicant class, chemical structure, pathological or physiological response, or other validated indices" of toxic response.[80] Linking these sets of data is currently one of the foremost goals of the toxicogenomics community.[81] Although researchers are making substantial progress in this direction, the relationship between gene expression and toxic impact is still uncertain in most cases.[82]

ii. Bioinformatics

Another formidable challenge facing toxicogenomics is the efficient management of the vast amount of information produced

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[78] Schmidt, *supra* note 50, at A23 (noting that the particular gene expression could indicate harmful, harmless, or protective effects).
[79] Waters, *supra* note 24, at 17 (listing several tissue pathologies and enzyme level changes as examples of "well-defined, conventional indices of toxicity").
[80] NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, GOALS OF THE NCT, *at* http://www.niehs.nih.gov/nct/goal1.htm (last visited Oct. 18, 2003) (on file with the North Carolina Journal of Law & Technology). "For example, experiments can be designed to correlate gene expression patterns with liver pathologies such as hepatomegaly (enlarged liver), hepatocellular necrosis (death of liver cells or tissues) or inflammation. It is also possible to look for correlative patterns—for example in enzyme levels—in liver and other tissues or cells such as blood. Changes in serum enzymes provide diagnostic markers of organ function that are commonly used in medicine and in toxicology." *Id.*
[81] Waters, *supra* note 24, at 17.
[82] Schmidt, *supra* note 50, at A23.

from microarrays.[83] In addition to simultaneously monitoring tens of thousands of genes, a number of other factors make data analysis more complex.[84] For example, the gene expression of a previously unexposed animal following an acute dose of a single toxin may be markedly different from that of an animal that is exposed to multiple toxins or that has developed an immune or other adaptive response based on previous exposures to the same or similar toxins. With the expected onslaught of toxicogenomics research during the next decade, bioinformatics will be a critical tool that researchers will use to better manage the complex data generated from such studies.[85]

IV. Admissibility of Toxicogenomics Evidence

A. The *Frye* Standard

Following a 1923 decision by the Court of Appeals for the D.C. Circuit,[86] most state and federal courts addressed any proffer of scientific evidence by asking whether the methodology used to

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[83] Hamadeh, *supra* note 23, at 232.

[84] Schmidt, *supra* note 50, at A23.

> People are generally exposed to many compounds simultaneously, often on a chronic or intermittent basis. Eventually . . . toxicogenomics will have to address more realistic exposure scenarios. These pathways are much more complex . . . . Any evaluation of chronic exposures must contend with the added dimensions of time, adaptive response, and cellular repair. "The signals for each of these processes are masked in the complexity of the response . . . ." "With repeat dosing, it all becomes much more intricate."

Id.

[85] Waters, *supra* note 24, at 20; Hamadeh, *supra* note 23, at 232.

> Bioinformatics in gene expression analysis deals with tasks including spot location, definition, and intensity calculations from raw scanned images, transformation of data sets into more easily quantifiable forms, application of analysis tools to extract associations between gene expression levels, and extraction of information from analyses that facilitate the development of new testable hypotheses.

Hamadeh, *supra* note 23, at 232.

[86] Frye v. United States, 293 F. 1013 (D.C. Cir. 1923).

generate that evidence was "sufficiently established to have gained general acceptance in the particular field in which it belongs."[87] While this "*Frye* standard" is intuitively satisfying since it leaves the judgment of what constitutes quality science up to the scientific community, critics have attacked the *Frye* standard from three directions. First, the standard under *Frye* would necessarily exclude new or novel scientific evidence, regardless of its actual reliability or relevance.[88] Second, the vagueness of the *Frye* language gave courts too much control over admitting or excluding evidence.[89] And third, at least in federal courts, *Frye* did not conform to the Federal Rules of Evidence enacted in 1975.[90]

B. *Daubert* and Federal Rule of Evidence 702

In 1993, the Supreme Court announced a new evidentiary standard for the federal courts[91] in *Daubert v. Merrel Dow Pharmaceuticals, Inc.*[92] The key change under *Daubert* is that judges now are required to act as gatekeepers, deciding whether

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[87] *Id.* at 1014.

[88] Craig Lee Montz, *Trial Judges as Scientific Gatekeepers After Daubert, Joiner, Kumho Tire, and Amended Rule 702: Is Anyone Still Seriously Buying This?*, 33 UWLA L. REV. 87, 92 (2001).

[89] *Id.*

[90] *Id.*

[91] *See* Joseph T. Walsh, *The Evolving Standards of Admissibility of Scientific Evidence*, 26(3) JUDGES J. 33, 35 (1997) (explaining that "[t]he Supreme Court's ruling in *Daubert* was issued under its supervisory power and thus is binding only on federal courts"). For several interesting attempts at describing how states have reacted to *Daubert*, s*ee* Joseph G. Eaton, *Survival of the "Fryest": A review of Recent Supreme Court Decisions Analyzing Frye's General Acceptance Standard and a 50 State Survey of the Standards for Admissibility of Expert Testimony*, TOXICS L. REP. 8 (2002) (listing 17 states that have "explicitly adopted" *Daubert* and noting that several other states apply a similar standard); Montz, *supra*, note 88, at 96 (stating that by 1997, twenty eight states were using *Daubert* or a similar standard); Alice B. Lustre, Annotation, *Post-Daubert Standards for Admissibility of Scientific and Other Expert Evidence in State Courts*, 90 A.L.R. 5th 453 (2001) (listing twenty-six states which apply *Daubert* or a similar test); Bert Black, *Expert Evidence in the Wake of the Daubert-Joiner-Kumho Trilogy*, ALI-ABA CONT. LEG. EDUC. 125 (1999) (listing twenty-two states as having adopted *Daubert*).

[92] 509 U.S. 579, 587–88 (1993).

"an expert's testimony both rests on a reliable foundation and is relevant to the task at hand."[93] Shortly after *Daubert* was decided, two additional Supreme Court decisions further clarified the new standard. In *General Electric Co. v. Joiner*,[94] the Court held that appellate courts must apply the abuse of discretion standard when reviewing a trial court's decision to admit or exclude testimony under *Daubert*. In *Kumho Tire Co. v. Carmichael*,[95] the Court held that *Daubert* was applicable to all expert testimony and not limited to scientific expert testimony. Together, these three cases comprise what has been called either "*Daubert* and its progeny" or simply the "trilogy."[96] The trilogy is now largely codified as Federal Rule of Evidence 702:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data,

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[93] *Id.* at 597–98. *Daubert* requires the judge to

> determine if the evidence to be admitted (1) qualifies as scientific knowledge, and (2) will aid the jury. Deciding whether the evidence qualifies as scientific knowledge is a question of *reliability*, in which the judge considers: (a) "whether [the theory or technique] can be (and has been) tested;" (b) "whether the theory or technique has been subjected to peer review and publication;" (c) "the known or potential rate of error;" and (d) "general acceptance" of the method. The second prong of the *Daubert* test is one of *fit*; the judge must decide if the evidence is relevant to the jury's determination of an issue of fact.

Callahan, *supra* note 10, at 151.

[94] 522 U.S. 136 (1997).

[95] 526 U.S. 137 (1999).

[96] *See* Margaret A. Berger, *Upsetting the Balance Between Adverse Interest: The Impact of the Supreme Court's Trilogy on Expert Testimony in Toxic Tort Litigation*, 64 LAW & CONTEMP. PROBS. 289 (2001); Catherine E. Brixen & Christine E. Meis, *Codifying the "Daubert Trilogy": The Amendment to Federal Rule of Evidence 702*, 40 JURIMETRICS J. 527 (2000); Lorie S. Gildea, *Sifting the Dross: Expert Witness Testimony in Minnesota After the Daubert Trilogy*, 26 WM. MITCHELL L. REV. 93 (2000).

> (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.[97]

1. Application of the Trilogy to Toxicogenomics Evidence

Some commentators have observed that while *Daubert* may "appear to establish a clear standard of admission, in application it has proved cumbersome."[98] The difficulty of applying *Daubert* is particularly apparent "in toxic tort litigation, where proof of medical causation is heavily dependent on expert scientific testimony."[99]

At least one commentator has argued that evidence produced from molecular epidemiology studies should be admissible in toxic tort litigation under *Daubert*.[100]

> Molecular epidemiology attempts to evaluate the damage done by toxic substances by looking for certain markers of exposure. Molecular epidemiological research involves finding new markers and determining the 'right' marker to measure a particular toxin. These markers or biomarkers are based on the premise that there are several stages of molecular events that eventually lead to cancer.[101]

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[97] FED. R. EVID. 702.

[98] Callahan, *supra* note 10, at 156–57.

[99] *Id.*

[100] *Id.* at 151.

[101] *Id.*

> Biomarkers can be used to indicate exposure from a particular toxin at three stages of events: (1) internal dose of the toxin, seen in products of the breakdown of the toxin called metabolites, (2) molecular dose seen in the presence of an adduct, a metabolite bonded to another molecule in the body, or (3) early signs of disease in the form of mutations and other damaging genetic effects.

Id.

Molecular epidemiology is thus similar to toxicogenomics since both fields attempt to directly link exposure to injury via molecular markers.[102]

i. General Causation

As previously stated,[103] to prove general causation, epidemiological evidence often is required *unless* there are "controlled experimental studies tying the toxin to the disease."[104] Such studies would be more valuable to toxic tort litigants than standard epidemiological studies that do not establish a direct causal link but merely serve to statistically demonstrate that "the occurrence of the disease is more common among those exposed to the toxin than those who are not."[105] If molecular epidemiology and toxicogenomics data could directly tie a particular toxin to a specific injury, such evidence might supplant epidemiology studies altogether.

Assuming preservation of the status quo, however, the question becomes whether judges would allow such molecular evidence to establish general causation in lieu of standard epidemiology studies. Given the name of the discipline, some judges might view molecular *epidemiology* evidence favorably, and as just another type of epidemiology evidence. The "unknown rate of error" in the field, though, might also lead some judges to reject the evidence under *Daubert's* reliability prong.[106] Unlike molecular epidemiology evidence, however, toxicogenomics evidence likely would not be seen as just another type of epidemiology evidence, and it suffers from similar reliability problems.[107]

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[102] Marchant, *supra* note 21, at 330 (citing among others, Callahan, *supra* note 10, and stating that although "[t]here are no reported toxic tort cases to date in which toxicogenomic data have had a significant role. Legal commentators have, nevertheless, begun to focus on potential tort applications of genomic techniques.").
[103] *See supra* Part II.A, note 7.
[104] Callahan, *supra* note 10, at 161.
[105] *Id.*
[106] *Id.* at 161–62.
[107] Marchant, *supra* note 21, at 332.

Additionally, "[b]ecause techniques involved in microarray studies are not yet standardized, researchers face technical difficulties at different stages when performing" experiments with them.[108] Given the lack of standardization among researchers, the reliability of toxicogenomics studies at this point is difficult to surmise. With additional toxicogenomics testing, particularly in conjunction with and validated by classical toxicity studies,[109] however, courts might be more apt to look favorably upon such evidence.[110]

> There are many scientific and legal issues relating to the validation, quality control and significance of toxicogenomic data that remain to be addressed before the data should be applied in a non-research context. Toxic tort litigants have very little incentive to wait for these uncertainties to be fully resolved because, unlike scientists or regulators who have the luxury of revisiting their decisions, litigants are one-time players in a high-stakes game. Therefore, there will be temptation to use toxicogenomic data in toxic tort lawsuits prematurely, just as has occurred in the past with other types of novel scientific evidence.

Id.; *see also* Schmidt, *supra* note 50, at A25.

> Regulatory agencies are also grappling with toxicogenomics issues. In June 2002, the . . . (EPA) issued its first guidelines for using genomics data for the standard-setting process . . . . [T]he agency opined that toxicogenomics will potentially have an 'enormous impact on our ability to assess the risk from exposure to stressors and ultimately to improve our risk assessments,' . . . [b]ut 'the relationships between changes in gene expression and adverse effects are unclear a this time and may be difficult to evaluate.' . . . The . . . (FDA) is also closely watching . . . the field . . . [and concerned about] the difficulty of linking microarray results to adverse effects.

Id.

[108] Hamadeh, et al., *supra* note 23, at 239; *see also* Schmidt, *supra* note 50, at A23–25 (noting that at least one committee, the Health and Life Sciences Institute of the International Life Sciences Institute (ILSI), rejected adopting standardized methods at this point since "[t]he techniques are still evolving at a rapid pace" and adopting such standards might constrain research efforts).

[109] *See supra* Part III.3.B. ¶ 2.

[110] Kyle Kolaja, *Toxicogenomics: Where Are We and Where Do We Go Now?*, GENOMICS PROTEOMICS, Sept. 2002, 11.

> Most preclinical toxicogenomic work to date has been either database building with prototype nondevelopment candidates

ii. Individual Causation

Regarding individual causation,[111] both molecular epidemiology and toxicogenomics move beyond the differential diagnosis paradigm of merely ruling out other potential causes of the disease, since they seek to demonstrably link a particular toxin to a particular disease. Since "[m]olecular epidemiological studies establish that certain toxins cause specific molecular and genetic changes that eventually lead to [disease], . . . these changes could be used as markers for exposure to the toxin."[112] The presence or absence of such a marker would seemingly be valuable individual causation evidence. Similarly, in toxicogenomics, "DNA microarrays could be used to identify or confirm the category of toxic substances to which an individual was exposed, based on gene expression profiling."[113] The expression or the absence of expression of certain genes in an individual could eventually serve as evidence to either establish or rebut the claim that exposure to a particular toxin caused the specific injury.

iii. Admissibility

As an emerging science capable of producing remarkably complex evidence, the admissibility of toxicogenomics data in toxic tort litigation still is an open question.[114] At this point,

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> or discovery-stage screening of compounds. A significant step forward will be the use of toxicogenomics data in studies intended to support registration. Currently, the FDA is leery of the use of data in this format, but it may be acceptable if the data support conclusions based on other classical endpoints of toxicity.

Id.

[111] *See supra* Part II.B.

[112] Callahan, *supra* note 10, at 148.

[113] Marchant, *supra* note 21 ("A key toxicogenomic technique is to profile (using a DNA microarray or 'gene chip') the cell-wide changes in gene expression following exposure to toxins. This approach creates the potential to provide a molecular 'fingerprint' of exposure or toxicological response to specific classes of toxic substances.").

[114] A Westlaw search of all federal and state cases on October 21, 2003 for "toxicogenomic!" or "microarray!" returned only two cases. Neither case

however, judges would be well advised to deem toxicogenomics evidence inadmissible based on relevancy until more research linking gene expression pathways to specific toxic endpoints is available.[115]

V. Conclusion

Dealing with causation in toxic tort litigation is currently a frustrating and cumbersome process for all parties involved. With the emergence of toxicogenomics, litigants soon may be able to trace discrete gene pathways from exposure to injury, thereby more definitively establishing or ruling out a causal connection between the particular substance and the specific injury in the plaintiff. Given the developmental stage of the science, however, judges controlled by *Daubert* must closely scrutinize any proffer of toxicogenomics evidence to ensure that it has been sufficiently linked to known toxicity endpoints.

involved the introduction or attempted introduction of toxicogenomics evidence to establish causation in a toxic torts case. Both pertained to disputes involving microarray manufacturers.

[115] Waters, *supra* note 24, at 15 (describing the progress and goals of the National Center for Toxicogenomics CEBS Knowledge Base that will ultimately combine data from a number of disciplines within one searchable database).