Supreme Court of the State of New York
Appellate Division: Second Judicial Department

D32285
H/prt

_____AD3d_____ Argued - May 6, 2011

WILLIAM F. MASTRO, J.P.
JOHN M. LEVENTHAL
LEONARD B. AUSTIN
JEFFREY A. COHEN, JJ.

2010-01450 OPINION & ORDER

Margalit Ratner, appellant, v
McNeil-PPC, Inc., respondent.

(Index No. 48820/02)

APPEAL by the plaintiff, in an action to recover damages for personal injuries, as limited by her brief, from so much of an order of the Supreme Court (Leon Ruchelsman, J.), dated January 19, 2010, and entered in Kings County, as granted the defendant's motion to preclude the plaintiff's expert testimony relating to the plaintiff's theory of medical causation and for summary judgment dismissing the amended complaint.

Weitz & Luxenberg, P.C., New York, N.Y. (Alani Golanski, Paul Pennock, and Lawrence Goldhirsch of counsel), for appellant.

Dechert LLP, New York, N.Y. (Robert W. Sparks, Debra D. O'Gorman, Patrick G. Broderick, Michael E. Planell, and Rose L. Amandola of counsel), for respondent.

LEVENTHAL, J. This case involves the admissibility, pursuant to *Frye v United States* (293 F 1013), of a plaintiff's experts' assertion that there is a causal connection between the plaintiff's ingestion of a ubiquitous over-the-counter medication and her subsequent development of a disease. Specifically, we consider a novel theory of medical causation concerning

the relationship between the long-term use of acetaminophen and the development of liver cirrhosis, where such theory is primarily, if not exclusively, supported by extrapolation from a few observational case studies. For the reasons discussed below, we conclude that the Supreme Court properly granted the defendant's motion to preclude the plaintiff's expert testimony relating to the plaintiff's theory of medical causation and for summary judgment dismissing the amended complaint.

The plaintiff testified at her deposition that beginning in 1985, she ingested Tylenol and Extra Strength Tylenol as needed in order to relieve migraine headaches. Tylenol is an over-the-counter analgesic which contains acetaminophen as its sole active ingredient. The plaintiff asserts that her usage never exceeded the maximum recommended dosage. In 1997 the plaintiff underwent a liver biopsy based upon symptoms of "portal hypertension," which did not show established cirrhosis.

In 2001 a magnetic resonance imaging exam indicated that the plaintiff had "micronodular cirrhosis." In July 2004 the plaintiff underwent liver transplant surgery. Thereafter, the plaintiff was diagnosed with "incomplete septal cirrhosis" (hereinafter ISC), a condition that reflected either an ongoing injury or a regression of liver scarring. In addition, the plaintiff was diagnosed with "hepatoportal sclerosis" (hereinafter HPS), a relatively uncommon liver condition which can lead to the shrinking of the liver and the development of "portal hypertension."

The plaintiff commenced this action against the defendant, which manufactures and sells Tylenol. In the amended complaint, the plaintiff sought to recover damages for negligence, failure to warn, defective design, breach of implied and express warranties, and a violation of the General Business Law.

Expert Disclosures

During discovery, the plaintiff disclosed that the following experts were prepared to testify on her behalf: Douglas Dieterich, Neil Theise, Gerald M. Rosen, and Suzanne Parisian. The plaintiff further revealed that two of her experts were prepared to set forth the theory that acetaminophen caused her liver cirrhosis. The plaintiff's experts asserted that acetaminophen was a known hepatotoxin, a substance that is harmful to the liver, and that repeated exposure to acetaminophen can cause chronic inflamation which can lead to fibrosis, or scarring of the liver, which may then cause liver cirrhosis. In support of their contentions, the plaintiff's experts relied

upon, inter alia, various medical studies, and the plaintiff's liver pathology slides, clinical history, and biopsy reports.

Dieterich, a gastroenterologist and a hepatologist, was prepared to testify that the toxic effects of acetaminophen could be seen at doses that were "only slightly greater than recommended therapeutic doses," and that people who are fasting, malnourished, or "predispos[ed]" are at a greater risk of acetaminophen toxicity, even at therapeutic doses. Dieterich opined that, after "ruling out other possibilities" and analyzing "the evidence using techniques consistent with those that he use[d] in his practice," to a reasonable degree of medical and scientific certainty, the plaintiff's cirrhosis was caused or substantially contributed to by acetaminophen. In support of his contentions, Dieterich relied upon, among other things, four case studies performed on mice and rats.

Theise, a pathologist and professor of hepatopathology, planned to testify about how exposure to hepatotoxins can result in toxic hepatitis, which can then lead to the development of hepatic fibrosis and liver cirrhosis. Theise would rely upon scientific publications and literature which he asserted indicated that acetaminophen could cause hepatitis, fibrosis, and cirrhosis. After reviewing the plaintiff's liver slides, he noted a pattern of scarring and nodularity consistent with a diagnosis of ISC. Theise found that the plaintiff's ISC indicated a regression of scarring and attributed this regression to the plaintiff's discontinuation of acetaminophen approximately three years prior to her 2004 liver transplant.

Rosen, a pharmacologist, would testify that the defendant failed to provide an adequate warning to consumers about the hepatotoxicity of acetaminophen, and that had methionine or other compounds been added as an ingredient to Tylenol, the hepatotoxicity of acetaminophen would have been effectively eliminated. Lastly, Parisian, a former chief medical officer with the Food and Drug Administration, would testify that the defendant had downplayed the potential risks posed by the hepatotoxicity of Tylenol, and failed to design, test, label, and market Extra Strength Tylenol to consumers in a reasonably prudent and safe manner.

The Defendant's Motion to Preclude and for Summary Judgment

Following discovery, the defendant moved to preclude the plaintiff's expert testimony relating to the plaintiff's theory of medical causation and for summary judgment dismissing the amended complaint. The defendant argued that the plaintiff's experts' opinion that acetaminophen can cause cirrhosis of the liver or contributed to the plaintiff's cirrhosis did not satisfy the standard

for admissibility of scientific evidence, and should be excluded under *Frye v United States* (293 F 1013). In support of the motion, the defendant relied upon the opinion of Howard J. Worman, a physician specializing in the fields of hepatology and cell biology. In an affidavit, Worman conceded that acetaminophen is toxic to the liver in overdose and that "in cases of massive overdose, acetaminophen can cause acute liver failure." However, Worman averred that the theory that long-term acetaminophen use at therapeutic doses can cause cirrhosis was not generally accepted in the medical and scientific communities. He defined cirrhosis as fibrosis or scarring of the liver, with widespread nodules of regenerating cells, which can lead to liver failure.

Worman asserted that the plaintiff's experts' opinions were based upon a faulty conclusion on the nature of her diagnosis. According to Worman, the plaintiff was actually diagnosed with HPS, rather than cirrhosis. In support, Worman relied upon a medical study published in 2007, in which he identified the plaintiff as "patient 7," and where that patient was found to have, among other things, ISC and HPS. That study made no mention of acetaminophen. Worman contended that the cause of HPS was unknown, and that HPS with ISC had never been attributed to acetaminophen use in scientific or medical literature.

Worman contended that the medical literature that the plaintiff's experts relied upon consisted almost exclusively of case reports and animal studies about acetaminophen overdose, and that such data about overdoses could not be extrapolated to explain the cause of the plaintiff's condition. Worman supplemented his affidavit with, inter alia, two medical articles which concluded that acetaminophen was safe in therapeutic doses, even for individuals suffering from liver disease.

The Plaintiff's Opposition

In opposition, the plaintiff argued that the defendant's motion should be denied because there was nothing novel in the methodologies employed by her experts, and that a *Frye* hearing was unnecessary. In an affidavit, the plaintiff averred that she stopped using Tylenol in 2001 or 2002 when she was informed that her liver condition was the result of Tylenol use; it was then that she was placed on a liver transplant list. The plaintiff asserted that she would never have used Tylenol if she had been warned about its dangers. She stated that she did not have the means to pay for a costly *Frye* hearing and submitted additional statements from her proposed experts.

Theise opined that chronic, daily use of the maximum therapeutic dose of acetaminophen contributed significantly to the need for the plaintiff's liver transplant. Theise

conceded that extrapolations from injuries in rodents to humans could not be made in terms of the likelihood and range of injuries, but that such injuries in rodents were indicative of the range of possibilities that one might expect in humans. He argued that even a clinical study with hundreds of patients would be insufficient to make a determination as to idiosyncratic toxicities of acetaminophen. He asserted that only after the accumulation of numerous individual case studies linking acetaminophen to cirrhosis, could epidemiologic studies be conducted to address that data, leading "clinicians [to] become more aware of the possibility of idiosyncratic drug reactions and a consensus builds around the link." Overall, Theise opined, within a reasonable degree of scientific certainty, that there was a significant, potential cumulative impact of consistent, repetitive use of even therapeutic doses of acetaminophen over a long term, indicating a cause of the plaintiff's injury. He asserted that clinical trials were not required to show causation arising from repetitive, long-term acetaminophen use, and that drug toxicities and cirrhosis could not be expected to appear in such clinical trials.

Theise cited to Harrison's Textbook of Medicine which, as early as 1987, showed that in a few patients prolonged use or repeated administration of acetaminophen in therapeutic doses led to development of chronic active hepatitis (liver injury characterized by inflammation) and cirrhosis. He stated that the fact that such cases were uncommon reflected that chronic daily use was also rare, that the absence of case reports was likely due to the absence of chronic exposures, and that the likelihood of such continual daily use was increasingly minimized by the use of other drugs. Further, Theise opined that, in all likelihood, there were host variations which modified the ways patients respond to acetaminophen. Theise cited a specific scientific study involving mice which, he argued, supported the use of animal studies to understand and predict human liver toxicity as measured by elevations in certain liver enzymes.

Theise disagreed with Worman's characterization of the plaintiff's condition and noted that the plaintiff was diagnosed with both HPS and ISC. Further, Theise asserted that ISC is "recognized as largely being the regression of cirrhosis." Theise acknowledged that the plaintiff was a patient in the 2007 HPS study cited by Worman, but stated that, given the radiological demonstration of the plaintiff's cirrhosis in 2001, along with the clinical symptoms of endstage liver disease that one does not generally see in HPS alone, that cirrhosis was established and seemed to have regressed precisely with the withdrawal of her acetaminophen use in 2001.

By way of a differential diagnosis, Theise determined that there were three

explanations for the concurrence of HPS and cirrhosis offered in the scientific literature: the first was that HPS and cirrhosis were independent lesions and unrelated diseases; the second was that cirrhosis was a late stage of HPS; and the third was that HPS predisposes individuals to subsequent development of cirrhosis, with regression of cirrhosis if the cause is removed. Theise stated that Worman was correct that there were no reports that HPS was associated with chronic acetaminophen use. However, Theise opined that in the absence of any other known cause of cirrhosis, and in the presence of a hepatotoxin, the finding of both HPS and cirrhosis in the plaintiff's liver did not undermine the likelihood that acetaminophen played a significant role in her endstage liver disease.

Dieterich asserted that, as a hepatotoxin, acetaminophen can cause toxic hepatitis, a non-viral liver inflammation. He added that repeated exposure to a hepatotoxin can lead to chronic toxic hepatitis. Further, Dieterich stated that chronic hepatitis can lead to liver fibrosis (scar tissue), and that extensive liver fibrosis can cause liver cirrhosis. Therefore, Dieterich opined, acetaminophen can result in liver cirrhosis.

In support, Dieterich cited to a 1988 case study which reported the case of a 48-year-old woman with cryptogenic cirrhosis, who took four to five grams of acetaminophen every day for five months. The authors concluded that acetaminophen's role in the patient's centrilobular injury was clear, but its role in cirrhosis was not. Dieterich also cited to a 2007 case study of a 60-year-old man with cirrhosis who took an average of six grams of acetaminophen daily for 14 years. The authors commented that the case suggested that liver fibrosis could develop in patients using acetaminophen for a long time at doses slightly exceeding the therapeutic dose range.

In addition, Dieterich relied upon a 1977 study by G. Kenneth Johnson and Keith G. Tolman (hereinafter the Johnson study) which reported the case of a 59-year-old woman who took 2,925 mg of acetaminophen daily for approximately one year, and who had a histological pattern typical of chronic aggressive hepatitis with cirrhosis. A 1983 study by, among others, S. Itoh (hereinafter the Itoh study) reported the case of a 53-year-old man in whom viral, alcoholic, and other metabolic injuries were excluded. Dieterich asserted that these studies, in conjunction with other evidence, illustrated that acetaminophen use can result in cirrhosis.

Dieterich stated that when the plaintiff's explanted liver was examined, it exhibited HPS with ISC. ISC, he contended, was a condition recognized as a stage in the regression of cirrhosis. According to Dieterich, this was consistent with the plaintiff's discontinuation of acetaminophen several years before undergoing the liver transplantation in 2004. Dieterich noted

that the plaintiff was less than 55 years old at the time of the cirrhosis diagnosis, she had no history of alcohol abuse and was not obese or diabetic, and that she had no risk factors for cirrhosis other than the use of acetaminophen. She was not taking any other medications and she did not have hepatitis C. Dieterich opined that the plaintiff's HPS did not alter the fact that she had cirrhosis that substantially contributed to both her injuries and the need for a liver transplant.

Parisian, a pathologist, submitted an affidavit in which she asserted that the defendant had the ability to improve Tylenol product labeling and marketing to improve safety. She added that consumers were not warned that there were potential differences in risk to the liver as a result of taking regular strength versus extra strength Tylenol. Both strengths failed to warn consumers that long term use could cause liver injury or that the risk was greater for the extra strength version. Further, Parisian stated that there was a design defect in Tylenol and that alternative, safer designs were available in Britain and Holland. Similarly, Rosen submitted an affidavit in which he averred that an alternate design could have made acetaminophen safer.

The Order Appealed From

In an order dated January 19, 2010, the Supreme Court, inter alia, granted the defendant's motion in its entirety. The Supreme Court determined that the defendant met its burden by demonstrating that there was no evidence linking acetaminophen to cirrhosis. The Supreme Court stated that there were no studies or medical literature concluding that the ingestion of normal doses of acetaminophen caused cirrhosis, and that the plaintiff was attempting to draw a medical parallel between the ingestion of proper doses and excessive doses to conclude that acetaminophen caused cirrhosis. The Supreme Court stated that almost all of the case reports involved the ingestion of doses greater than the recommended dose, or involved a patient who had a disease other than cirrhosis. With respect to Theise's affidavit, the Supreme Court noted that he had referred to the plaintiff's condition as "uncommon." The Supreme Court stated that Theise's conclusion was not accepted within the medical community.

The Supreme Court concluded that the plaintiff had failed to introduce any studies, peer reviewed articles, professional literature, judicial opinions, or recognized textbooks that set forth the plaintiff's experts' novel premise that the normal ingestion of acetaminophen can cause cirrhosis. The Supreme Court stated that without supporting material, the plaintiff failed to satisfy the evidentiary requirements of *Frye.*

Frye

At issue in this case is the admissibility of the plaintiff's experts' opinions relating to the plaintiff's novel theory of medical causation. New York courts, applying the *Frye* test (*see Frye v United States,* 293 F 1013), permit expert testimony based on scientific principles, procedures, or theories only after the principles, procedures, or theories have gained general acceptance in the relevant scientific field (*see Parker v Mobil Oil Corp.,* 7 NY3d 434, 446; *People v Wesley,* 83 NY2d 417, 422; *Cumberbatch v Blanchette,* 35 AD3d 341, 342; *Zito v Zabarsky,* 28 AD3d 42). A *Frye* inquiry addresses the question of "whether the accepted techniques, when properly performed, generate results accepted as reliable within the scientific community generally" (*People v Wesley,* 83 NY2d at 422; *Marso v Novak,* 42 AD3d 377, 378 [internal quotation marks omitted]). The burden of proving general acceptance rests upon the party offering the disputed expert testimony (*see Cumberbatch v Blanchette,* 35 AD3d at 342; *Zito v Zabarsky,* 28 AD3d 42; *Del Maestro v Grecco,* 16 AD3d 364; *Saulpaugh v Krafte,* 5 AD3d 934, 935; *Lara v New York City Health & Hosps. Corp.,* 305 AD2d 106). "[W]hile courts will go a long way in admitting expert testimony deduced from a well-recognized scientific principle or discovery, the thing from which the deduction is made must be sufficiently established to have gained general acceptance in the particular field in which it belongs" (*Frye v United States,* 293 F at 1014).

"[G]eneral acceptance does not necessarily mean that a majority of the scientists involved subscribe to the conclusion. Rather it means that those espousing the theory or opinion have followed generally accepted scientific principles and methodology in evaluating clinical data to reach their conclusions" (*Zito v Zabarsky,* 28 AD3d at 44 [internal quotation marks omitted]; *see Marsh v Smyth,* 12 AD3d 307, 311 [stating, in concurrence by Saxe, J., that the "*Frye* test emphasizes 'counting scientists' votes, rather than . . . verifying the soundness of a scientific conclusion" (some internal quotation marks omitted)]).

The *Frye* test typically considers the admissibility of new scientific tests, techniques, or processes (*see People v Wesley,* 83 NY2d at 437 [noting that the trial court's *Frye* hearing was "virtually the first in the Nation to consider whether forensic application of DNA analysis had been generally accepted as reliable"]; *see also Selig v Pfizer, Inc.,* 185 Misc 2d 600, 606 ["the majority of New York cases in which a *Frye* standard has been applied involve the admissibility of obviously novel forensic and social science techniques"], *affd* 290 AD2d 319; *Blackwell v Wyeth,* 408 Md 575, 971 A2d 235 [applying *Frye* test to preclude the plaintiffs' hypothesis that a substance in childhood

vaccines can cause neurological defects, such as autism, since the plaintiffs' experts' fields of expertise were not relevant to the specific bodies of science related to autism and its causes]). For example, in *Frye*, the Court of Appeals of the District of Columbia considered the introduction of evidence based on a "systolic blood pressure deception test," a test which purportedly functioned by measuring fluctuations in blood pressure (*Frye v United States,* 293 F at 1013). In finding that the systolic blood pressure deception test was inadmissible, the court stated that the test "ha[d] not yet gained such standing and scientific recognition among physiological and psychological authorities as would justify the courts in admitting expert testimony deduced from the discovery, development, and experiments thus far made" (*id.* at 1014).

The *Frye* test has also been applied to determine the admissibility of expert testimony based on new social and behavioral theories. In *People v Wernick* (89 NY2d 111), the Court of Appeals affirmed the preclusion of a defendant's expert testimony regarding "neonaticide syndrome," a term used to describe a mother killing her newborn within 24 hours of birth, on the ground that the behavioral theory was not established as generally accepted in the profession as reliable (*see People v LeGrand,* 8 NY3d 449 [finding trial court erred in precluding defendant's expert from providing psychological testimony on the reliability of eyewitness identifications]; *People v Taylor*, 75 NY2d 277, 286 [affirming admission of expert testimony regarding "rape trauma syndrome" after concluding "that the relevant scientific community has generally accepted that rape is a highly traumatic event that will in many women trigger the onset of certain identifiable symptoms"]).

Nevertheless, where there is no novel or innovative science involved, or where the tendered scientific deduction has been deemed generally accepted as reliable, there remains a separate inquiry applied to all evidence. This inquiry is "whether there is a proper foundation--to determine whether the accepted methods were appropriately employed in a particular case" (*Parker v Mobil Oil Corp.,* 7 NY3d at 447; *see People v LeGrand,* 8 NY3d at 457 [once the general reliability concerns of *Frye* are satisfied, the court will consider whether there is a proper foundation for the reception of the evidence at trial]; *People v Wesley,* 83 NY2d at 429).

Hence, where a plaintiff's qualified experts offer no novel test or technique, but intend to testify about a novel theory of causation, where such opinion is supported by generally accepted scientific methods, it is proper to proceed directly to the foundational inquiry of admissibility, which is whether the theory is properly founded on generally accepted scientific

methods or principles (*see Parker v Mobil Oil Corp.*, 7 NY3d at 447 [explaining that because "(t)here is no particular novel methodology at issue for which the Court needs to determine whether there is general acceptance . . . the inquiry here is more akin to whether there is an appropriate foundation for the experts' opinions"]; *People v Garrow*, 75 AD3d 849, 852 [*Frye* hearing was not required because expert testimony offered by the prosecution did not involve any novel procedures or innovative scientific theory]; *Nonnon v City of New York*, 32 AD3d 91, *affd* 9 NY3d 825 [in action where plaintiffs alleged that elevated levels of toxic substances at Pelham Bay Landfill caused their injuries, the court held that plaintiff's experts' testimony, based upon deductions of epidemiologist and toxicologists, was not novel and therefore admissible without a *Frye* hearing]; *see also Marsh v Smyth*, 12 AD3d at 312-313 [in concurrence by Saxe, J., stating "(u)nlike a newly developed test or process, a (novel) theory about the mechanism of an injury will not prompt the profession generally to weigh in with its own studies or publications on the subject"; thus, "to require proof . . . that a propounded theory of causation is accepted by a substantial percentage of the profession, would be to impose a virtually insurmountable hurdle"]).

Discussion

The plaintiff argues that the Supreme Court erred in precluding her experts' theory of causation, and thereupon awarding summary judgment to the defendant dismissing the amended complaint. She asserts that the studies and case reports addressed the long term use of acetaminophen and found the potential for serious life-threatening liver injury. The defendant does not dispute that acetaminophen is a hepatotoxin and has been associated with liver failure in certain cases of massive overdose, nor does the defendant dispute the credentials of the plaintiff's experts. Instead, the defendant asserts that there is no scientific support for the general theory that acetaminophen taken within recommended doses can cause cirrhosis of the liver and, therefore, that there is no support for the specific theory that the plaintiff's cirrhosis is attributable to acetaminophen (*see generally Parker v Mobil Oil Corp.*, 7 NY3d at 448 ["It is well-established that an opinion on causation should set forth a plaintiff's exposure to a toxin, that the toxin is capable of causing the particular illness (general causation) and that plaintiff was exposed to sufficient levels of the toxin to cause the illness (specific causation)"]).

As the plaintiff correctly contends, her proffered experts have not utilized any novel scientific techniques or evidence. Rather, the plaintiff's experts seek to set forth the novel theory

that therapeutic acetaminophen use caused the plaintiff's liver cirrhosis primarily based upon the fact that acetaminophen is a hepatotoxin and that certain case studies suggest a relationship between acetaminophen and cirrhosis.

Generally, deductive reasoning or extrapolation, even in the absence of medical texts or literature that support a plaintiff's theory of causation under identical circumstances, can be admissible if it is based upon more than mere theoretical speculation or scientific hunch (*see Zito v Zabarsky,* 28 AD3d at 46; *see also* Black's Law Dictionary [9th ed 2009] [defining "extrapolation" as "(t)he process of estimating an unknown value or quantity on the basis of the known range of variables" and "(t)he process of speculating about possible results, based on known facts"]). Deduction, extrapolation, drawing inferences from existing data, and analysis are not novel methodologies and are accepted stages of the scientific process.

For example, in *Zito v Zabarsky* (28 AD3d 42), this Court expressly recognized that extrapolation or deduction is warranted in instances where the theory pertains to a new drug. In *Zito,* the plaintiff alleged that the defendant physician departed from accepted medical practices by prescribing an excessive dose of the drug Zocor, causing the plaintiff to develop polymyositis, an autoimmune condition. At a *Frye* hearing, the plaintiff's experts pointed to the temporal relationship between the plaintiff's drug ingestion and injury, the "accepted scientific theory of the dose/response relationship" (*id.* at 46), and cited one article where a patient had developed an autoimmune disease that was likely induced by simvastatin, the generic name for Zocor. The trial court precluded the plaintiff's experts on the basis that no medical literature expressly reported a causal nexus between an excessive dose of Zocor and the onset of polymyositis.

On appeal, this Court reversed, holding that "[t]he fact that there was no textual authority directly on point to support the experts' opinion [was] relevant only to the weight to be given the testimony, but does not preclude its admissibility" (*id.*). This Court explained that "[w]ith the plethora of new drugs entering the market, the first users of a new drug who sustain injury because of the dangerous properties of the drug or inappropriate treatment protocols will be barred from obtaining redress if the [*Frye*] test were restrictively applied" (*id.*; *see Lugo v New York City Health & Hosps. Corp.*, _____AD3d_____, 2011 NY Slip Op 06475 [2d Dept 2011] [where the Supreme Court determined that the testimony of the plaintiffs' experts that the infant plaintiff's brain injuries were caused by an episode of severe neonatal hypoglycemia lasting 81 minutes was inadmissible, this Court disagreed, finding that the Supreme Court had applied the *Frye* test too

restrictively given that hypoglycemia can cause brain injury, that certain infants are more susceptible than others to neurologic injury, and that hypoglycemia is a toxic and dangerous state with no safe level]; *DieJoia v Gacioch,* 42 AD3d 977, 978 [holding that the trial court applied the *Frye* test too restrictively in precluding plaintiff's expert based "almost exclusively on the fact that he could not produce any medical literature" to support the precise theory of causation, specifically "that cardiac catheterization has ever caused thrombosis and, subsequently, paralysis"]).

Nevertheless, "[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered" (*General Elec. Co. v Joiner,* 522 US 136, 146; *see Blackwell v Wyeth,* 408 Md 575 [finding that the analysis of data or extrapolation requires more than mere conjecture to pass reliability scrutiny]). As discussed below, we find that the data upon which the plaintiff's experts relied is insufficient to support their novel theory of medical causation, rendering that theory speculative.

Before the Supreme Court, the plaintiff adduced only two case reports of individuals that linked therapeutic usage of acetaminophen and the development of liver cirrhosis in otherwise healthy subjects. The Itoh study reported the case of a 53-year-old man in whom viral, alcoholic, and other metabolic injuries were excluded. Over the course of 12 years, the man ingested 12-20 tablets per day of a drug which contained 58 mg of acetaminophen and 5 mg of codeine; a biopsy revealed micronodular cirrhosis. The Johnson study, entitled "Chronic Liver Disease and Acetaminophen," reported the case of a 59-year-old woman who took 2,925 mg of acetaminophen daily for one year. Approximately one month before entering a hospital, the woman developed anorexia and "easy fatigability." The woman had a histological pattern typical of chronic aggressive hepatitis with cirrhosis.

"Courts have recognized that . . . observational studies or case reports are not generally accepted in the scientific community on questions of causation" (*Heckstall v Pincus,* 19 AD3d 203, 205 [precluding expert's opinion where plaintiff presented "no clinical or epidemiological data or peer reviews" linking the drug to the disease, and supported claim of causation solely with case reports]; *see Pauling v Orentreich Med. Group,* 14 AD3d 357 [save for the plaintiff's expert's own unpersuasive observational studies, the plaintiff failed to submit any medical literature to support existence of a novel disease]). We note that the two aforementioned case studies relied upon by the plaintiff constitute merely observational data which are of a lesser caliber than controlled clinical studies from which results can be reviewed and verified. Moreover,

even taking the two case studies at face value, they do not unequivocally state that acetaminophen caused the liver cirrhosis observed therein. In this regard, the Johnson study specifically stated that "[t]he role of acetaminophen ingestion in this patient's liver disease is uncertain." The two studies merely hypothesized that the liver injuries sustained by the patients therein were related to ingestion of therapeutic doses of acetaminophen and that further study was warranted. Moreover, the analytical gap between the plaintiff's scientific data and her experts' theory of causation is widened by the contrary scientific articles submitted by the defendant which, among other things, concluded that acetaminophen is safe in therapeutic doses, even for individuals suffering from liver disease.

This case is distinguishable from *Zito* because, among other things, acetaminophen is not a new drug. For over 50 years, acetaminophen has been widely available without a prescription. The record is replete with evidence showing that the effects of acetaminophen on the human liver has been studied extensively. Indeed, Dieterich, the plaintiff's expert, acknowledges that acetaminophen "has been the subject of thousands of journal articles and a vehicle for extensive research into hepatotoxicity."

The singular clinical study that the plaintiff relies upon to connect therapeutic acetaminophen ingestion to the development of cirrhosis is a 2006 study by, among others, Paul B. Watkins. This study involved the development of a product which combined hydrocodone and acetaminophen. The study was prematurely ceased once it was found that 31% to 44% of the healthy adults who ingested the maximum recommended dose of acetaminophen had serum alanine aminotransferase levels (hereinafter ALT) (a liver enzyme) that were greater than 3 times the upper limit of normal (hereinafter the ULN) and marked elevations (14 times and 16 times the ULN) in several subjects. However, this clinical study does not support the plaintiff's theory of causation, since it states that the clinical importance of the ALT elevations was unclear, and the authors of the study did not interpret the finding of raised ALT levels to be indicative of serious liver injury. Indeed, the authors found that "acetaminophen clearly has a remarkable safety record when taken as directed, and chronic treatment with 4 g daily has been confirmed to be safe."

The speculative nature of the plaintiff's experts' theory of causation is exemplified by a review of the 2007 HPS study, in which the defendant identified the plaintiff as "patient 7." While that study indicated that the plaintiff's presumed liver disease was cryptogenic cirrhosis, the authors of the study wrote, "[t]he scarcity of reported cases of HPS requiring [a liver transplant] may be because of the fact that this unusual entity may often go unrecognized and be classified as

cryptogenic cirrhosis." Further, we note that this study does not even mention acetaminophen, much less draw a correlation between the plaintiff's condition and her use of acetaminophen.

The plaintiff did not put forward any clinical or epidemiological data or peer reviewed studies showing that there is a causal link between the therapeutic use of acetaminophen and liver cirrhosis. Consequently, it was incumbent upon the plaintiff to set forth other scientific evidence based on accepted principles showing such a causal link. We find that the methodology employed by the plaintiff's experts, correlating long term, therapeutic acetaminophen use to the occurrence of liver cirrhosis, primarily based upon case studies, was fundamentally speculative (*see Lewin v County of Suffolk,* 18 AD3d 621), and that there was too great an analytical gap between the data and the opinion proffered. We emphasize that when an expert seeks to introduce a novel theory of medical causation without relying on a novel test or technique, the proper inquiry begins with whether the opinion is properly founded on generally accepted methodology, rather than whether the causal theory is generally accepted in the relevant scientific community. Here, the plaintiff failed to meet that burden.

Thus, the Supreme Court did not err in granting that branch of the defendant's motion which was to preclude the plaintiff's expert testimony relating to the plaintiff's theory of medical causation, and thereupon granting that branch of the defendant's motion which was for summary judgment dismissing the amended complaint.

Accordingly, the order is affirmed insofar as appealed from.

MASTRO, J.P., AUSTIN, and COHEN, JJ., concur.

ORDERED that the order is affirmed insofar appealed from, with costs.

ENTER:

Matthew G. Kiernan
Clerk of the Court