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ARTICLES

THE TRIGGER OF COVERAGE FOR CANCER: WHEN DOES GENETIC MUTATION BECOME “BODILY INJURY, SICKNESS, OR DISEASE”?

Donald T. Ramsey*

I. INTRODUCTION

Cancer is a disease defined by the presence of cells that have acquired the ability to replicate endlessly and form tumors that invade surrounding tissue.¹ As a result of startling scientific advances over the last ten years,² cancer is now known to develop according to a multi-stage process³ that

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1. See BERT VOGELSTEIN & KENNETH W. KINZLER, *THE GENETIC BASIS OF HUMAN CANCER* xvii (1998).

2. Vogelstein and Kinzler point out:

As late as the 1970's human cancers remained a black box. Theories were abundant: Cancer was hypothesized to result from defective immunity, viruses, dysregulated differentiations, mutations. . . . [I]t was difficult to be optimistic that cancer would soon be understood. . . . This has changed dramatically as a result of the revolution in cancer research that has occurred in the last decade. If this revolution were to be summarized in a single sentence, that sentence would be '*Cancer is, in essence, a genetic disease.*'

Id. at xv (emphasis added).

3. The classic description of multistage development includes the phases of initiation, promotion, and progression. In this paradigm, *initiation* occurred with a genetic mutation that was, in itself, insufficient to cause cancer. To cause cancer these initiated cells had to be exposed to *promoters* which appeared to stimulate growth in the initiated cells but did not seem to be mutagenic themselves. Cancer still would not develop, however, until the cells reached the stage of *progression*, at which point they exhibited rapid growth,

begins with the mutation of a gene in a single cell.⁴ In this process, four to seven key genes within a cell must mutate before a malignant tumor appears.⁵ Such mutations can result from infinitesimally tiny alterations in molecules of DNA at a subcellular level. Since the mutation of one of the cell's important genes is a rare event, there may be long intervals between mutations, and it typically takes many decades before a malignant tumor appears.⁶ Despite the rarity of any particular mutation, cancer is a common condition of modern man. Virtually everyone would get cancer if they lived long enough.⁷

Plaintiffs in toxic tort suits and product liability actions frequently allege that their cancer was caused by exposure to a chemical or toxin. Resultant requests for insurance coverage by product manufacturers and other industrial defendants will require insurers to decide at what point "cancer" becomes "bodily injury, sickness, or disease," and thus, a covered "occurrence" under general liability policies. Though insureds undoubtedly will contend that a continuous trigger should govern these coverage determinations, certain general features common to most types of cancer, and the desire of courts to find a "factual" basis for the continuous trigger, make this proposition problematic.

The continuous trigger, and what some consider to be its functional equivalent, the "injury-in-fact" trigger of coverage, are the predominant methods for determining insurance coverage for progressive or continuous injuries or diseases under general liability policies.⁸ Though they have been

increased invasiveness, and metastases. See J. MICHAEL BISHOP & ROBERT A. WEINBERG, *MOLECULAR ONCOLOGY* 43-45 (1996); HENRY C. PITOT, *FUNDAMENTALS OF ONCOLOGY* 140, 163 (1986).

4. See MALCOLM ALISON & CATHERINE SARRAF, *UNDERSTANDING CANCER* 37 (1997).

5. See ROBERT A. WEINBERG, *ONE RENEGADE CELL: HOW CANCER BEGINS* 47 (1998).

6. See *id.* at 143.

7. See *id.* at 156.

8. See Mitchell Lathrop, *Tobacco-Related Litigation: How It May Impact the World's Insurance Industry*, 3 CONN. INS. L.J., 305, 359 (1997) ("While there are a number of competing 'trigger of coverage' theories, the so-called 'continuous trigger' or 'triple trigger' appears to be today's majority view in the case of latent or progressive bodily injury."); *Montrose Chem. Corp. of Cal. v. Admiral Ins. Co.*, 10 Cal. 4th 645, 673, 687 n.22 (1995) ("[T]he weight of authority . . . is that bodily injury and property damage that is continuous or progressively deteriorating throughout successive CGL policy periods, is

guided by a variety of rationales,⁹ most courts that have adopted a continuous trigger have made its use dependent, in whole or in part, on whether “in fact” the “bodily injury, sickness, or disease” to the third-party claimant was continuous through successive policy periods.¹⁰ In making “injury” a question of fact, courts have intentionally disregarded or inadvertently ignored definitional questions about what constitutes “injury.”¹¹ In simple cases this is not a problem. Once the “injury” lies outside the realm of the self evident, however, as it does in the context of latent disease processes like those at work in the development of cancer,

potentially covered by all policies in effect during those periods.”); see also Michael G. Doherty, Comment, *Allocating Progressive Injury Liability Among Successive Insurance Policies*, 64 U. CHI. L. REV. 257, 261 (1997).

9. These include administrative convenience. See *Northern States Power Co. v. Fidelity & Cas. Co.*, 523 N.W.2d 657, 662-63 (Minn. 1994) (maximizing coverage, ambiguity in policy language); *Keene Corp. v. Ins. Co. of N. Am.*, 667 F.2d 1034, 1041 (D.C. Cir. 1981) (the “plain meaning” of the policy, and the drafting history); *Montrose*, 10 Cal. 4th at 673, 688. See generally James M. Fischer, *Insurance Coverage for Mass Exposure Tort Claims: The Debate Over the Appropriate Trigger Rule*, 45 DRAKE L. REV. 625, 649-50 (1997).

10. Under traditional tests, the time of an occurrence is when the bodily injury or property damage happens, not when the wrongful act took place. See *Remmer v. Glens Falls Indem. Co.*, 140 Cal. App. 2d 84, 88 (1956); BARRY L. OSTRAGER & THOMAS R. NEWMAN, HANDBOOK ON INSURANCE COVERAGE DISPUTES § 9.03(a) (10th ed. 2000). “Recently, many courts that have adopted a continuous trigger theory have done so in combination with an injury-in-fact definition of bodily injury that has defined bodily injury so broadly as to effectively duplicate the multiple trigger tort.” Fischer, *supra* note 9, at 647.

11. At least one court has rejected the injury-in-fact trigger in favor of a simpler and easier to administer “exposure” trigger even though it acknowledged “the attraction of the intellectual honesty of the injury-in-fact approach, which is arguably the truest to the CGL policy language of ‘bodily injury’ (not relying, as a proxy for ‘real injury’ on either diagnosis or subclinical tissue damage), which . . . might not develop into full blown disease.” *Guaranty Nat’l Fire Ins. Co. v. Azrock Indus., Inc.*, 205 F.3d 253, 264 (5th Cir. 2000). Another court, in a case involving exposure to welding fumes and asbestos, has attempted to deal with this kind of factual complexity by developing a “flexible continuing injury trigger,” a hybrid of the continuing injury and injury-in-fact triggers.

A ‘continuing injury’ trigger applies those policies in effect at any time from exposure through manifestation, while an ‘injury-in-fact’ trigger applies those policies which were in effect at any time when actual injury occurred. In effect, we find that the proper trigger is a *hybrid* between these two triggers. The *hybrid* is a ‘flexible continuing injury’ trigger that presumes uniformity of injury probability while allowing ‘injury-in-fact’ evidence to rebut the presumption and constrict the range of the allocation field.

Lincoln Elec. Co. v. St. Paul Fire & Marine Ins. Co., 210 F.3d 672, 690 n.24 (6th Cir. 2000).

courts are without a standard by which to judge whether a particular insult to the body, or a series of subcellular changes, is "injurious" during any particular policy period. In part the problem is legal; in part it is scientific. The New Jersey Supreme Court summed it up well in *Owens-Illinois, Inc. v. United Insurance Co.*¹²

Our concepts of legal causation were developed in an age of Newtonian physics, not of molecular biology. Were it possible to know when a toxic substance clicks on a switch that alters irrevocably the composition of the body and before which no change has "occurred" we might be more confident that occurrence-causing damages had taken place during a particular policy period. The limitations of science in that respect only compound the limitations of law.¹³

The remarks of the *Owens-Illinois* court are significant, not just because they are insightful, but because they reflect a traditional "all or nothing" view, prevalent in the context of asbestos coverage litigation, that looks for "irrevocable" changes as the hallmark of undefined "injury." Through the 1980s and 1990s, asbestos-related injury cases served as the model by which courts judged other continuing injury cases and the triggers applicable to them.¹⁴ In such cases, the continuing injurious presence of asbestos fibers in the lung tended to blur or moot questions about whether the courts applied the continuous trigger because the exposure to asbestos was continuous, because the injury grew progressively and measurably worse over time, or because the original injury simply persisted for a period of years. The ineradicable nature of asbestos fibers and their "irrevocably" injurious presence (i.e., the "exposure-in-residence," as the court in *Keene Corp. v. Insurance Co. of North America*¹⁵ described it) meant that injury of some kind was ongoing from the moment the first fiber was inhaled until the claimant died. Thus, successive policies were triggered

12. 650 A.2d 974 (N.J. 1994).

13. *Id.* at 985.

14. Courts also applied the continuous trigger to bodily injury in a variety of other contexts, including DES. See *Eli Lilly & Co. v. Home Ins. Co.*, 482 N.E.2d 467 (Ind. 1985) (breast implants); *Dow Corning Corp. v. Hartford Accident & Indem. Co.*, No. 93-325-788-CK (Mich. Cir. Ct. Nov. 16, 1994) (lead paint); *Chantel Assocs. v. Mount Vernon Fire Ins. Co.*, 656 A.2d 779 (Md. App. 1995).

15. 667 F.2d 1034 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1007 (1982).

regardless of whether the particular disease at issue was pleural plaques, asbestosis, bronchogenic carcinoma, or mesothelioma.¹⁶

But not all latent or insidious diseases are characterized by the continuing presence of the toxic agent in the body. For such diseases, a continuous trigger may be factually insupportable even though these illnesses are marked, like asbestos-related diseases, by a long latency period that separates first exposure from the appearance of clinical symptoms. Some cancers fall within this group.

A malignant tumor results when a cell accumulates a series of mutations to key genes that control the cell's growth and repair functions. A cell is prone to accumulate such mutations over time because the genes within a cell not only sustain new mutations from time to time, but the mutations that are sustained pass down from one generation of cells to the next in the process of cell division and replication.¹⁷ Accordingly, the cells in a malignant tumor will carry exact copies of the original key mutation that first appeared decades earlier.¹⁸ Thus, the development of cancer is, in this sense, continuous. The difficulty is that the terms "injury," "sickness," and "disease" cannot appropriately be used to describe all phases of this process. Consequently, use of the term "continuous" tends to mislead because it is not appropriate to say that an "injury" or "disease" is occurring through the entire thirty to fifty year interval between the initial key genetic mutation and the ultimate development of a malignant mass of cells.

Thirty-three to forty percent of all people will develop cancer at some point in their lives.¹⁹ Most people who do get cancer do not become ill until they are in their sixties or seventies.²⁰ Because it typically takes three to five decades or

16. In applying a continuous trigger to asbestos-related bodily injury in the Coordinated Asbestos Coverage Cases, the trial court stated: "The foregoing conclusions apply regardless of which asbestos-related disease affects the claimant and regardless of which type of asbestos fiber was inhaled by the claimant." *In re Asbestos Ins. Coverage Cases*, Judicial Council Coordination Proceeding No. 1072, Statement of Decision Concerning Phase III Issues, slip op. at 43 (Cal. App. Dep't Super. Ct. Jan. 24, 1990).

17. See BISHOP & WEINBERG, *supra* note 3, at 35-37.

18. See *id.*

19. See WEINBERG, *supra* note 5, at 141; DENNIS W. ROSS, INTRODUCTION TO ONCOGENES AND MOLECULAR CANCER MEDICINE 58 (1998).

20. See ALISON & SARRAF, *supra* note 4, at 37-41.

more from the time of the first mutation for a cell to accumulate the requisite number of mutations for cancer to arise, labeling all phases in the development of cancer as "injury" or "disease" means that almost half of the population is deemed to be injured or diseased throughout most of their lives. The use of the term "injury" or "disease" is inappropriate because even people who die from some other cause, before they can develop cancer, carry many thousands of cells bearing mutations to key genes throughout most of their existence.²¹ Thus, if genetic mutation amounts to injury and disease, then injury is universal and disease is a normal aspect of being alive.

Consideration of these factors alone should preclude any automatic application of a continuous trigger to all phases of cancer development. But there are additional problems as well. Unlike the presence of asbestos fibers in the lung, genetic damage induced by mutagens, is not, strictly speaking, "irrevocable." Genetic damage, if minor, may be repaired.²² If such damage is too extreme, it may trigger the death of the cell.²³ Unlike mutations caused by asbestos fibers which lodge in the lung because they are inhaled from outside the body, other genetic mutations can and do occur spontaneously as part of the body's normal process.²⁴ Thus, for multiple reasons, and depending upon the particular type of cancer, the terms "injury" and "disease" fail properly to describe all phases in the complex etiology of cancer, which, especially in its long "early" phase of development is "a dynamic process that may stop temporarily, or permanently, revert to normality, or progress to frank neoplasia."²⁵ Indeed, the development of cancer is at once both too rare and too common, too normal and too exceptional, for all stages of the entire process comfortably to bear the designation "bodily injury, sickness, or disease."

Because of this complexity, courts must resist the temptation to lump all cancers together, or to model all applications of the continuous trigger on the example of

21. See Henry C. Pitot, *Multistage Carcinogenesis*, in *ENCYCLOPEDIA OF CANCER*, vol. II, at 1613 (1997).

22. See WEINBERG, *supra* note 5 at 90.

23. See *id.* at 126.

24. See ROSS, *supra* note 19, at 22.

25. C. SONNENSCHIN & A.M. SOTO, *THE SOCIETY OF CELLS* 101 (1998).

asbestos-related injury. Although courts have sought to avoid defining "injury" and to be guided simply by the "facts," courts should acknowledge that this effort is untenable when the issues involve a series of astonishingly complex events that unfold through the interactions of vanishingly infinitesimal subcellular molecules over the course of an entire lifetime.

This article does not attempt to posit any comprehensive, "proper" definition of "injury, sickness, or disease."²⁶ With more modest goals in mind, it attempts to emphasize three significant ideas:

(1) The determination as to whether injury is "continuous," and thus whether multiple policies are triggered, may turn on whether the carcinogen is absorbed by, and remains actively present in the body after exposure to it in the outside atmosphere ceases;

(2) The enduring character of the developmental processes at work must be balanced against, and may be outweighed by the reality that over long periods of time the process is also marked by significant discontinuity, the lack of any "new" injury and the great likelihood that the disease will never develop;

(3) The exponential increase in knowledge about the molecular, genetic basis of cancer may soon yield screening techniques that permit scientists and physicians to pinpoint when a tumor becomes malignant, or at least

26. Dictionary definitions of injury, sickness, and disease define these words in terms of impairment, damage, destruction, and ill health.

Injury: 1a: an act that damages, harms or hurts: an unjust or undeserved infliction of suffering or harm . . . 2: hurt, damage, or loss sustained. *Syn.* Injury, hurt, damage, harm and mischief mean in common the act or result of inflicting on a person or thing something that causes loss, pain, distress or impairment or destruction of right, health, freedom, soundness, or loss of something of value.

WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE UNABRIDGED 648 (Merriam-Webster 1896). "*Sickness*: 1a: the condition of being ill: ill health: illness. b: a disordered, weakened or unsound condition . . ." *Id.* at 1164.

Disease: 1a: *obs.* lack of ease . . . b(1): an impairment of the normal state of the living animal or plant body or of any of its components that interrupts or modifies the performance of the vital functions, being a response to environmental factors (as malnutrition, industrial hazards, or climate), to specific infective agents (as worms, bacteria or viruses), to inherent defects of the organism (as various genetic anomalies), or to combinations of these factors: sickness, illness.

Id. at 2111.

to better estimate when cancer becomes a genuine probability instead of an unpredictable chance.

Courts that seek a factual basis for the use of a continuous or injury-in-fact trigger must thus look carefully at the particular etiology of the cancer at issue before they apply a coverage trigger. In addition, courts faced with coverage questions in cancer cases should look for and take advantage of new advances in cancer screening techniques where they are available. And where such tools are unavailable, courts should abide by what *is* known before adopting presumptions of disease or fictions of injury as a means of supplying a "factual" basis for the continuous trigger.

II. CASES JUSTIFY A CONTINUOUS TRIGGER BY THE PRESENCE OF CONTINUING INJURY THROUGH SUCCESSIVE POLICY PERIODS

Guided by its belief that the "heart" of an insurance transaction is "the insured's purchase of certainty," the court in *Keene Corp. v. Insurance Co. of North America*,²⁷ was the first court to impose a continuous trigger.²⁸ The court was remarkably candid about its lack of concern for the factual basis of "injury" in successive policy periods. According to the *Keene* court, "the details of the development of these [asbestos-related] diseases [were] not relevant to the issues decided."²⁹ Indeed, according to the court in *Keene*, "if a disease could be predicted to develop many years after inhalation of asbestos, yet no cellular changes were known to occur during that period, we would still hold that all policies are triggered from the point of exposure to the point of manifestation."³⁰

As if embarrassed by the *Keene* court's result-oriented approach to coverage and its disregard for the actual facts of injury, courts that have adopted a continuous trigger after *Keene* have made much greater efforts to justify the continuous trigger by the existence of actual continuing injury throughout successive policy periods. "Nothing in the policy language purports to exclude damage or injury of a

27. 667 F.2d 1034 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1007 (1982).

28. *See id.*

29. *Id.* at 1038 n.3.

30. *Id.* at 1044 n.19.

continuous or progressively deteriorating nature," said the court in *Montrose Chemical Corp. of California v. Admiral Insurance Co.*,³¹ "as long as it occurs during the policy period."³² Under this standard, the court further explained "whether the damages and injuries alleged are, in fact, 'continuous' is itself a matter for final determination by the trier-of-fact."³³

Courts adopting an injury-in-fact trigger of coverage likewise focus on the issue of whether, "in fact," an injury occurred in each successive policy period. In *American Home Products Corp. v. Liberty Mutual Insurance Co.*,³⁴ the Second Circuit affirmed the district court's determination that coverage under the policy required "a showing of actual injury, sickness or disease occurring during the policy period, based upon the facts proved in each particular case."³⁵ Though the court of appeals rejected the district court's conclusion that an injury had to be "diagnosable" or "compensable" to qualify as an injury, it affirmed that "the trigger of coverage clause unambiguously provides for coverage based upon the occurrence during the policy period of an injury-in-fact."³⁶

But what is the nature of the "injury" that must, in fact, "be present" during the policy period in order to trigger coverage? Case law rarely states what the nature of the injury is, and when it does, the definitions are often simplistic or circular.³⁷ The *Keene* court, which had already dispensed

31. 10 Cal. 4th 645, 673 (1995).

32. *Id.*

33. *Id.* at 694.

34. 748 F.2d 760 (2d Cir. 1984).

35. *Id.* at 763 (quoting *American Home Prods. Corp. v. Liberty Mut. Ins. Co.*, 565 F. Supp. 1485, 1489 (S.D.N.Y. 1983)).

36. *Id.*

37. Other commentators have noted this same problem and criticized the tendency of courts to assume that they can avoid the definitional question by making "injury" a "question of fact":

Courts that adopt the injury in fact theory do not at all answer the question of what constitutes a bodily injury. . . . [E]ven if the medical evidence that shows that microscopic injuries occur upon inhalation of asbestos or upon first exposure to some drug is accepted as unproblematic, this medical "injury" evidence *itself* does not and cannot constitute a definition of bodily injury in the CGL policy. There is no principle—metaphysical, linguistic, hermeneutical, or other—by which physical facts alone determine meanings.

James E. Scheuermann, *The Injury in Fact Theory as a Solution to the Trigger of Coverage Issue*, 24 TORT & INS. L.J. 763, 775-76 (1989).

with the need to see "facts," was equally hostile to common definitions of "injury." The *Keene* court not only rejected the definitions of injury developed in workers' compensation cases, statute of limitations cases, and health insurance cases, but also held that neither the definition of injury followed by physicians, nor that subscribed to by laypersons, was controlling.³⁸

The court in *E.R. Squibb & Sons, Inc. v. Accident & Casualty Insurance Co.*,³⁹ viewing the question of injury in the context of DES⁴⁰ cases, also did not see any difficulty: "[T]he term 'injury' is plain on its face—it involves any form of harm which befalls a person adversely affected by the product involved. . . . Hence, no extrinsic evidence concerning the meaning of the term need be considered."⁴¹

In response to the insurers' arguments that the trial court had mistaken mere subclinical cellular changes for actual "injury" caused by asbestos, the California appellate court in *Armstrong World Industries v. Aetna Casualty & Surety Co.*⁴² offered two solutions. First, though the court framed the "key question" as "the point in time at which injury takes place,"⁴³ the court thereafter explained that as long as an injury eventually did become evident in subsequent years, it was unnecessary to pinpoint exactly when it occurred. "For purposes of determining insurance coverage, absolute precision is not required as to when the injury occurred."⁴⁴ Second, in response to the insurers' argument that some form of impairment, and not mere cellular change, was necessary for "injury" to occur, the court held it sufficient that at a microscopic level the physiological processes associated with the inhalation of asbestos "impair the gas exchange function of the lung cells" almost

38. See *Keene Corp. v. Insurance Co. of N. Am.*, 667 F.2d 1034, 1043-44 (D.C. Cir. 1981), cert. denied, 455 U.S. 1007 (1982).

39. 853 F. Supp. 98 (S.D.N.Y. 1994).

40. DES, or diethylstilbestrol, was a synthetic estrogen prescribed to pregnant women in the 1950s and 1960s to prevent miscarriages. Years later the drug was discovered to cause reproductive system abnormalities and cancer to offspring who were exposed to DES in utero. See *Sindell v. Abott Labs.*, 26 Cal. 3d 588, 594 (1980).

41. *E.R. Squibb & Sons*, 853 F. Supp. at 100.

42. 52 Cal. Rptr. 2d 690 (Cal. Ct. App. 1996).

43. *Id.* at 700.

44. *Id.* at 704.

immediately upon the inhalation of asbestos fibers.⁴⁵

The difficulty in defining injury and determining when and for how long it occurs was troublesome enough when dealing with subclinical changes in tissue at the cellular level. The problem became more intense as courts attempted to apply fact-based standards of "injury," without any governing definition, to asbestos-related cancers, such as bronchogenic carcinoma or mesothelioma. In these types of cases, courts attempted to locate injury in the form of genetic change existent at the sub-cellular level decades before a tumor appears.

In *Stonewall Insurance Co. v. Asbestos Claims Management Corp.*,⁴⁶ for example, the Second Circuit preliminarily acknowledged that "in view of the different etiologies of asbestosis and cancer, it is possible to hold, as the district court did, that these two diseases trigger policies differently."⁴⁷ Then, focusing on the trigger for asbestos-related cancer, the appellate court found that the evidence was sufficient to support *both* the jury's finding of "injury-in-fact" during the long latency period leading up to tumor development, and the opposite conclusion of the district court, which had reversed the jury's conclusion and determined that injury did not, in fact, exist until a tumor appeared.⁴⁸ Fearing that the district court may have misapplied the injury-in-fact test, the Second Circuit remanded the question of continuous injury in asbestos cancer cases to the district court for further consideration.

On remand, the district court directly commented on the difficulty of the definitional-fact finding task and the peculiar notion of "injury" that was needed to fit the lengthy, complex process leading up to cancer within the confines of a continuous injury trigger:

As noted at the outset, the case requires us to force complex medical concepts into the words of insurance policies drafted by people who never contemplated this type of litigation. When most of us think of an injury, we consider some discrete insult to the body that causes immediate and observable injury—a broken leg, a stick in

45. *See id.*

46. 73 F.3d 1178 (2d Cir. 1995), *reh'g denied*, 85 F.3d 49 (2d Cir. 1996).

47. *Id.* at 1197.

48. *See id.*

the eye. When someone is diagnosed with cancer, we do not normally think of them having been injured repeatedly over the years in which the cancer was developing.⁴⁹

The conclusion that "injury" is a poor term to describe cancer development may create problems for many courts whose rules of policy interpretation require them to ascertain the "plain meaning" of policy language according to "the meaning a layperson would ordinarily attach to it."⁵⁰ According to this "plain meaning" test, if the term "injury" would not ordinarily be used to describe a subcellular event that happened forty years before cancer appeared, then that form of "injury" should not trigger insurance coverage for that time frame. But even though the district court in *Stonewall* acknowledged this problem, it concluded on remand that the continuing presence of asbestos fibers in the lung constituted a persistent and ongoing insult to surrounding tissue and directly caused or promoted mutations that eventually contributed to cancer. On this basis, the district court held in favor of the continuous trigger despite its acknowledgment that it could not tell "at what point in any particular case asbestos became involved in the process of cancer development."⁵¹ As the unpublished trial court opinion stated:

The medical testimony shows that asbestos can contribute to the cancer process in any of the following ways: 1) the process by which the body's immune system attacks

49. *Stonewall Ins. Co. v. Asbestos Claims Management Corp.*, No. 86 Civ. 9671(JSM), 1998 WL 405047, at *1 (S.D.N.Y. July 17, 1998).

50. *Waller v. Truck Ins. Exch., Inc.*, 11 Cal. 4th 1, 18 (1995). Indeed, a partial list of such states includes: Rhode Island (*Baccari v. Donat*, 741 A.2d 262 (R.I. 1999)); Wisconsin (*Moore v. Economy Fire & Cas. Co.*, 601 N.W.2d 853 (Wis. 1999)); Alaska (*Fejes v. Alaska Ins. Co.*, 984 P.2d 519 (Alaska 1999)), Idaho (*Mutual of Enumclaw Ins. Co. v. Pedersen*, 983 P.2d 208 (Idaho 1999)), Missouri (*Martin v. United States Fidelity & Guar. Co.*, 996 S.W.2d 506 (Mo. 1999)), Tennessee (*Barnes v. Employers Mut. Cas. Co.*, No. 03A01-9812-CH-00403, 1999 WL 366587 (Tenn. Ct. App. June 8, 1999)), Connecticut (*O'Brien v. United States Fidelity & Guar. Co.*, 669 A.2d 1221 (Conn. 1996)), Florida (*St. Paul Fire & Marine Ins. Co. v. Tingley Sys., Inc.*, 722 So. 2d 849 (Fla. Dist. Ct. App. 1998)), Washington (*State Farm Mut. Auto. Ins. Co. v. Ruiz*, 952 P.2d 157 (Wash. 1998)), Kansas (*Hammon v. Safeco Ins. Co.*, 954 P.2d 7 (Kan. Ct. App. 1998)), North Dakota (*Martin v. Allianz Life Ins. Co.*, 573 N.W.2d 823 (N.D. 1998)), Maryland (*Kendall v. Nationwide Ins. Co.*, 702 A.2d 767 (Md. 1997)), Utah (*Mesa Dev. Co. v. Sandy City Corp.*, 948 P.2d 366 (Utah Ct. App. 1997)).

51. *Stonewall Ins. Co.*, 1998 WL 405047, at *2.

asbestos at the time it invades a cell generates oxygen-free radicals which may (a) damage a cell's DNA, making the cell susceptible to mutation from asbestos or other environmental agents, e.g., tobacco smoke; (b) increase the rate of cell proliferation which increases the likelihood of spontaneous genetic mutation in otherwise healthy cells; (c) increase the rate of proliferation in already mutated cells causing the body to have an increased number of such cells, thereby increasing the risk of further mutation; 2) the asbestos fiber may itself lodge in a cell in a manner that a) causes a mutation; b) makes the cell susceptible to mutation; c) accelerates the rate of cell expansion, or d) reduces a cell's ability to prevent excessive expansion; and (3) the scarring process resulting from the body's removal of asbestos may itself contribute to the development of cancer.⁵²

Not all cancers, however, are like asbestos-related cancers. In fact, though courts have often followed the asbestos injury model in coverage litigation, they have repeatedly emphasized, in connection with virtually every other aspect of asbestos mass tort and insurance litigation, that the problems posed by asbestos are unique.⁵³ Indeed, asbestos-related cancers may be almost singularly unique in the degree to which they are initiated and promoted by the continuing presence of the asbestos fibers in the lung. For many other types of cancer, however, the offending agent responsible for the initial mutation of an important gene does not remain present in the body. Although cancer may develop, partially as a result of an initial genetic insult, the question of whether "bodily injury, sickness, or disease" can fairly be said to have been present from the moment of first key mutation to the development of a malignant tumor is much more problematic. In such circumstances, courts that look for "injury" in each policy period must confront the complexity of the actual facts and accord proper significance

52. *Id.*

53. "Courts generally view asbestos cases as unique in the law." *Wasau Tile, Inc. v. County Concrete Corp.*, 593 N.W.2d 445, 457 (Wis. 1999). "[T]he rule we develop in this case for subsequent damages is premised on the unique nature of the asbestos situation and is not applicable in other areas." *Carson v. Johns-Manville Sales Corp.*, 399 N.W.2d 1, 9 (Mich. 1986). "As other courts around the country have noted, asbestos cases are unique in the law." *San Francisco Unified Sch. Dist. v. W.R. Grace & Co.*, 44 Cal. Rptr. 2d 305, 308 (Cal. Ct. App. 1995).

to the important discontinuities that are present in the development of cancer.

More importantly, courts must question the extent to which the ongoing metabolic processes of life itself may be described as "injury" in any normal or ordinary use of that word. In a DES coverage case, *E.R. Squibb & Sons, Inc. v. Accident and Casualty Insurance Co.*,⁵⁴ the court does suggest that even the normal processes of life may be considered injury: "Where an event has continuing effects which continue to enhance the ill effects felt by the victim of the injury as a result of the amplification though otherwise normal bodily process or otherwise, the injury will be continuing so long as such effects continue."⁵⁵ Though this approach may be understandable, given the inability to map out the etiology of certain injuries in DES cases,⁵⁶ it is a dangerous principle to

54. 860 F. Supp. 124 (S.D.N.Y. 1994).

55. *Id.* at 126.

56. The problem of selecting the appropriate trigger may be especially difficult with respect to DES-related medical problems. DES (diethylstilbestrol) was a synthetic estrogen given to between two and four million women in the United States between 1938 and 1971. In 1971, it was discovered that it caused clear cell adenocarcinoma of the vagina in young women who were exposed in utero when their mothers took the drug. See R. Scully et al., *Vaginal and Cervical Abnormalities Including Clear-Cell Adenocarcinoma, Related to Prenatal Exposure to Stilbertral*, 4 ANNALS OF CLINICAL & LABORATORY SCI. 222 (1974). Since 1971, DES has been shown to be responsible for a broad array of medical problems in the mothers who took the drug and their daughters and sons, including adenosis (a pre-cancerous epithelial infirmity, cervical ridges or hoods, and other abnormal formations of the tissues of the cervix) as well as problems in the male reproductive organs. See *Harper v. Eli Lilly & Co.*, 575 F. Supp. 1359 (N.D. Ohio 1983). The exact mechanism of the development of clear-cell adenocarcinoma, however, is not well understood at this time. See RYAN ET AL., *KISTNER'S GYNECOLOGY AND WOMEN'S HEALTH* 87 (Mosby ed., 7th ed. 1999); M. Marselos & L. Tomatis, *Diethylstilbestrol: I, Pharmacology, Toxicology and Carcinogenicity in Humans*, 28A EUR. J. CANCER 1182, 1182-89 (1992).

Given this array of diseases and the unknown etiology of clear-cell cancer, it is not surprising that various courts have held DES-related diseases to be like asbestos-related diseases as well as *unlike* them. "AHP cannot rely on the rationale of cases that have found immediate injury from the ingestion of asbestos fibers, because the drugs at issue in this case differ markedly from asbestos in the manner in which they are alleged to injure humans." *American Home Prods. Corp. v. Liberty Mut. Ins. Co.*, 565 F. Supp. 1485, 1493-94 (S.D.N.Y. 1983), *aff'd in part*, 748 F.2d 760 (2d Cir. 1984). "Since an asbestos-related disease is similarly separated in time from its initial assault to the time of the manifestation of its debilitating effect, we see no reason not to adopt the same approach to DES-related diseases." *Vale Chem. Co. v. Hartford Accident & Indem. Co.*, 490 A.2d 896, 902 (Pa. Super. Ct. 1985).

This may, in turn, account for the broad variety of coverage triggers that courts have used in DES coverage cases. These include continuous trigger, see *Vale*

apply across the board to other cancers and diseases.

Courts applying the continuous trigger also urge that "the entire mosaic of events must be considered in order to ensure the accuracy of the legal characterization given to the situation."⁵⁷ When the "entire mosaic" is cancer, many of the facts that must be taken into account through the process of the development of the actual malignant tumor are more consistent with normal ongoing processes of molecular change through the course of living and aging than they are with accepted notions of injury, sickness, or disease.

III. PROBLEMS IDENTIFYING THE TIMING AND FACT OF "INJURY" IN THE DEVELOPMENT OF CANCER

A. Cancer—An Overview

Cancer is the generic term for a disease that has more than one hundred different forms.⁵⁸ Every different type of cell is vulnerable to its own forms of cancer.⁵⁹ All cancers, however, develop according to certain shared patterns and processes. The process starts with a genetic mutation originating in a single cell, which, over three to four decades or more, accumulates three to six more key mutations, leading to uncontrolled cell proliferation, tumor growth, and the invasion of adjacent tissue.⁶⁰ In its most virulent, lethal form it leads to metastases, i.e., the migration of mutated cells to other sites in the body where they establish other colonies of mutated cells and ultimately other tumors.⁶¹

The genetic mutations that occur as a result of exposure to a mutagen, or which occur spontaneously in the process of cell division, are acquired somatic cell mutations rather than inherited germ line mutations.⁶² Traditional genetics deal

Chem. Co., 490 A.2d 896; *Eli Lilly & Co. v. The Home Ins. Co.*, 482 N.E.2d 467 (Ind. 1985) (exposure and manifestation trigger); *Transamerica Ins. Co. v. Belafonte Ins. Co.*, 490 F. Supp. 935 (E.D. Pa. 1980) (manifestation); *American Motorist Ins. Co. v. E.R. Squibb & Sons, Inc.*, 406 N.Y.S.2d 658 (N.Y. 1978) (injury in fact); *American Home Prods. Corp.*, 565 F. Supp. 1485.

57. *E.R. Squibb & Sons, Inc. v. Accident and Cas. Ins. Co.*, 853 F. Supp. 98, 101 (S.D.N.Y. 1994).

58. See *What You Need to Know About Cancer*, SCI. AM. (Special Issue) Sept. 1996, at 3 [hereinafter SCI. AM.].

59. See VOGELSTEIN & KINZLER, *supra* note 1, at xvii.

60. See *id.*

61. See ALISON & SARRAF, *supra* note 4, at 110.

62. See *id.* at 37.

with traits that are passed along from one generation to the next due to genes present in the germ line cells which produce eggs and sperm. The genetics of cancer development, however, deal with somatic cells like those present in the epithelium,⁶³ lung, and colon. Thus, a genetic mutation that occurs to a liver cell in the course of a person's life will not be passed down to his or her descendants. In fact, relatively few cancers arise from inherited germ line mutations.⁶⁴

As noted earlier, cancer is primarily a disease of the elderly. The chances of contracting cancer escalate rapidly with age. "The log of the incidence rate and the log of age have a linear relationship, with the incidence increasing dramatically (10^3 - 10^7 -fold) with age."⁶⁵ At present, between thirty-three and forty percent of all people will contract cancer and half of those who contract it will die from it.⁶⁶ As people live longer, these percentages may increase.⁶⁷ Indeed, "given enough time cancer will strike every human body."⁶⁸ There are currently eight million people in the United States living with cancer and another approximately 1.2 million were expected to contract it in 1999.⁶⁹

The genes that sustain the mutations that ultimately lead to cancer are infinitesimally small and unbelievably complex. Each cell contains 70,000 to 100,000 genes which, if stretched out in a linear strand, would be two meters long.⁷⁰ If the cell nucleus, which is less than 1/1000th of an inch wide⁷¹ was magnified to the size of a basketball, the genetic

63. Epithelial cells are those in the sheet-like layer of tissue which covers and lines the internal and external surfaces of the body. They form the outer layer of the skin and other surface tissue such as the mucous membranes, which line such cavities as the mouth and the stomach. *See id.* at 238.

64. *See* ROSS, *supra* note 19, at 15; SHIRLEY W. HODGSON & EAMON R. MAHER, HUMAN CANCER GENETICS 1 (2d ed. 1999). "Germ line" cell mutations are those which "because of their presence in the germ line become hereditary, which, as the first step in multistage carcinogens predispose the individual to the development of cancer." ALISON & SARRAF, *supra* note 4, at 240. "Somatic" cell mutations are mutations "in diploid cells that are not cells of the germ line and thus do not undergo meiosis to form gametes thus the mutation is *not* inherited." *Id.* at 258.

65. VOGELSTEIN, *supra* note 1, at xviii.

66. *See* WEINBERG, *supra* note 5, at 141; ROSS, *supra* note 19, at 58.

67. *See* ALISON & SARRAF, *supra* note 4, at 1.

68. WEINBERG, *supra* note 5, at 156.

69. *See* THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM, NATIONAL CANCER INSTITUTE (1999).

70. *See* ROSS, *supra* note 19, at 5.

71. *See* MICHAEL WALDHOLZ, CURING CANCER 23 (1997).

strand containing the substance of heredity would be as thick as the thread of a spider's web and extend for 200 kilometers.⁷²

There are four basic categories of causes of the genetic mutations that may eventually lead to cancer—viral⁷³, hereditary,⁷⁴ environmental⁷⁵ (including lifestyle), and spontaneous⁷⁶. Estimates differ on the relative importance of each factor—in part because it is difficult to isolate factors and because each factor is of greater or lesser importance depending on the type of cancer in question. Cigarette smoking and a diet low in fruits and vegetables cause or significantly contribute to somewhere between one-half to two-thirds of all cancers.⁷⁷ Hereditary genetic mutations (in germline as opposed to somatic cells) cause five to ten percent of cancers.⁷⁸ Perhaps as many as fifteen percent of cancers stem from viruses, bacteria, or parasites.⁷⁹ While it is very difficult to calculate, air and water pollution are thought to account for only about two percent of fatal cancers.⁸⁰

Significantly, a relatively high percentage of cancers would occur simply because of the normal operation of the body's own metabolic processes, independent of "external"

72. See ROSS, *supra* note 19, at 4. If all the DNA present in a human body were stretched out it would reach from the earth to the sun and back again. See *Heredity, Molecular Genetics, DNA Replication* <<http://www.britannica.com/bcom/eb/article/4/0,5716,120934+4+111157,00.html>>.

73. Perhaps as many as 15% of cancers worldwide are traceable to viral causes. See SCI. AM., *supra* note 58. Of the viral carcinogenic agents "the two most important are the human papilloma viruses types 16 and 18, which are sexually transmitted and the Hepatitis B virus." *Id.* at 33.

74. Inherited mutations in genes can confer a very high risk of cancer. A predisposition to certain kinds of breast cancer, colon cancer, melanoma, kidney cancer, and retino blastoma can be inherited. See *id.* at 22.

75. The two leading "environmental" causes of cancer are tobacco smoke and poor diet consisting of high amounts of saturated fat. See *id.* at 28.

76. Some cancers occur simply because the body's own processes produce carcinogens and generate genetic errors that go unrepaired. See *id.* at 26. As Weinberg explains: "the cell's normal energy metabolism releases millions of highly reactive molecular by-products every day. Many of these are oxidants and 'free radicals,' the latter being unpaired highly reactive electrons. Like environmental mutagens, these indigenous molecules can chemically alter a variety of molecules including the cell's DNA." WEINBERG, *supra* note 5, at 88. See also SCI. AM., *supra* note 58, at 25-36.

77. See SCI. AM., *supra* note 58, at 27.

78. See HODGSON & MAHER, *supra* note 64, at 22.

79. See SCI. AM., *supra* note 58, at 33.

80. See *id.* at 32.

factors.⁸¹ Some experts estimate that perhaps a quarter of all cancers are “hard core”—they would develop even in a world free of all external carcinogens simply because of the production of carcinogens within the body and the occurrence of spontaneous unrepaired genetic damage that results in mutations.⁸²

Most malignant tumors begin with a single key mutation in a single ancestral cell. By the time a tumor becomes clinically evident, it will consist of a billion or more cells.⁸³ Each key genetic mutation is highly improbable—one chance per million cell divisions to activate one oncogene⁸⁴ and one chance in a billion cell divisions to inactivate both copies of a tumor suppressor gene.⁸⁵ Although there are thousands of cells containing one or multiple mutations at any given time, it often takes four decades or more after the first key genetic mutation occurs in a cell for the requisite number of additional mutations to occur and a malignant tumor to arise. This is the primary reason why cancer is a disease generally associated with the aging process.⁸⁶

Cancer results when a sufficient number of mutations have “hit” the important genes that control a cell’s replication and repair functions so that the cell reproduces endlessly, copying its mutated genetic blueprint over and over. The tumor that ultimately develops is thus linked to the original genetic mutation as well as to each of the series of mutations that accumulate in the cell thereafter. Though the tumor cell is the descendant of the cell whose genes sustained the first mutation, there may be hundreds or thousands of generations and many years between the ancestral cell that sustains the first key genetic alteration and the progeny cell that receives the second or third key event.

There are thus very significant intervals between the first mutation and the second, and between the second and the third. Following the second mutation, there may not be a

81. See DAVID S. SCHOTTENFELD & JOSEPH F. FRAUMENI, JR., *CANCER EPIDEMIOLOGY AND PREVENTION* 68 (2d ed. 1996).

82. See *SCI. AM.*, *supra* note 58, at 26; WEINBERG, *supra* note 5, at 57.

83. See WEINBERG, *supra* note 5, at 2.

84. See *id.* at 56, see also discussion *infra* notes 123-39 and accompanying text.

85. See *id.* at 71, 76.

86. See ROBERT A. WEINBERG, *RACING TO THE BEGINNING OF THE ROAD, THE SEARCH FOR THE ORIGIN OF CANCER* 251 (1996).

third. After the third mutation, there may not be a fourth. It is only the rare mutation to a key gene that ultimately contributes to cancer. In fact, scientists believe that there is "one fatal malignancy per 100 million billion cell divisions . . ."⁸⁷ Most genetic mutations in somatic cells are simply not related to cell growth or to a cell's internal repair function.⁸⁸ Often a genetic mutation will trigger the death of the cell and thus eliminate the possibility that this mutation will be carried forward in a daughter cell.⁸⁹ Thus, it is extremely rare for a cell that has acquired one mutation to a key gene to accumulate the three to six *additional* key mutations required for cancer to develop.

As indicated above, each type of cancer has its own unique genetic and pathological characteristics. The specific manner in which any particular cancer proceeds through mutational steps is not completely known, and because of the different genetic makeup, environmental influences, and lifestyle choices of different individuals, there are innumerable paths that may eventually lead to cancer. In order to discuss the development of cancer in any meaningful way, however, one must first understand how cells divide.

Before focusing on the submicroscopic process of cell division, however, it is useful first to pause momentarily and assess the implications of what is apparent at the macroscopic level. If one-third to two-fifths of all people eventually contract cancer, then defining injury to include all periods between the first key genetic mutation and the development of a malignant tumor yields a peculiar result. Under this definition, almost half the people would have to be classed as "injured" or "diseased" for virtually their entire lives—even though almost none of them had "cancer" until they were in their seventies. Is "injury" really a useful or proper term to characterize such a broad segment of the population? If up to forty percent of the population is deemed to be sick through eighty percent of their lives, then what does it mean to be normal? Indeed, the question is more complex because all people, even the people who do not contract "cancer" within their lifetimes, are always carrying within them thousands, if not tens or hundreds of thousands

87. WEINBERG, *supra* note 5, at 142.

88. *See id.*

89. *See discussion infra* notes 121-26 and accompanying text.

of cells that bear genetic mutations that are the same, only not as "advanced" as those that appeared as malignant tumors in the people with cancer.⁹⁰ Although these anomalies in the use of the term "injury" do not dictate any given result, nor help posit what definition of injury may best describe the development of cancers, they do begin to place the issue in perspective.

B. *The Genetic Code*

Cells are the basic building blocks of living things, and the human body has about thirty trillion cells.⁹¹ Each cell has a nucleus, and the nucleus of each cell contains twenty-two pairs of chromosomes, made up of DNA (deoxyribonucleic acid), plus the sex chromosomes XX or XY.⁹² Chromosomes are the structures upon which the hereditary instructions for each particular cell are arranged. DNA is a large molecule that carries the genetic information that cells need to replicate. DNA acts like an intricate, lengthy instruction manual or blueprint that tells each specific cell how to perform its particular function in the body.⁹³ The DNA found in each type of cell also instructs that cell how to reproduce a mirror image of itself.

DNA is arranged in segments of varying length and complexity called genes. The 70,000 to 100,000 genes in each cell are comprised of different combinations and sequences of three to six billion base pairs of four nucleotides, adenine ("A"), thymine ("T"), cytosine ("C") and guanine ("G").⁹⁴ These bases are paired together chemically (by hydrogen bonds) across the strands of the DNA double helix.⁹⁵ Adenine (A) is always paired with thymine (T), and guanine (G) is always paired with cytosine (C). Thus, "an A appearing in one strand of the helix always faces a T in the opposite strand; a C in one strand inevitably confronts a G in the other. So the sequence of ACCGGTCAA in one strand will be intertwined with a partner sequence, TGGCCAGCTT in the other."⁹⁶

Along the strands of the DNA these nucleotides are

90. See WEINBERG, *supra*, note 5 at 143, 156.

91. See SCI. AM., *supra* note 58, at 3.

92. See ROSS, *supra* note 19, at 4.

93. See *id.* at 7.

94. See *id.*; VOGELSTEIN & KINZLER, *supra* note 1, at 5.

95. See ROSS, *supra* note 19, at 4.

96. WEINBERG, *supra* note 5, at 9.

grouped together in sixty-four different three-letter combinations called codons.⁹⁷ The genetic code is governed by the order and sequence of these three-letter words along a strand of DNA. Each codon encodes for one or more of the twenty amino acids⁹⁸ used in the synthesis of proteins which are largely responsible for the structure and function of the human organism. Perhaps most important among these proteins are enzymes which function as biological catalysts and permit chemical reactions to occur very rapidly at normal life temperatures.⁹⁹

Different proteins are activated according to the instructions carried by the different sequences of base pairs read as three-letter codons. "The letters CTG, for instance, tell a cell to build the amino acid leucine and place it in a specific spot in forming a protein, while the sequence GAT describes aspartic acid."¹⁰⁰ Each gene is typically 30,000 base pairs long.¹⁰¹ There are 70,000 to 100,000 genes in each cell and almost every cell in the body carries the entire genome, i.e., all the genes necessary for the complete blueprint of the living organism.¹⁰² "The human genome is six billion base pairs long. If spelled out and written as a book, the human genome would be the size of a medical school library."¹⁰³ The loss of a single base in a sequence of codons in a gene, or the substitution of a T where a G should be, is enough to constitute a mutation of that gene.

C. Cell Division

When a cell divides, it attempts to make an exact copy of each of the chromosomes and genes contained within it. The cell cycle is divided into four phases, each with its own specialized characteristics:

G1 (Gap1) Phase: The Gap 1 phase is a period in which

97. See ROSS, *supra* note 19, at 6.

98. See *id.*

99. See *Hereditary, Molecular Genetics, DNA as an Information Carrier* (1999) <<http://www.britannica.com/bcom/eb/article/4/0,5716,120934+4+111157,00.html>>. The DNA does not convey these instructions to the proteins directly, but does so by means of messenger RNA (ribonucleic acid) and transfer RNA which effects the protein synthesis outside of the nucleus of the cell in the cytoplasm. See *id.*

100. WALDHOLZ, *supra* note 71, at 23.

101. See ROSS, *supra* note 19, at 7.

102. See WEINBERG, *supra* note 5, at 6-7.

103. ROSS, *supra* note 19, at 7.

the cell increases in size and prepares to duplicate its DNA by producing the necessary proteins for DNA synthesis.

S (Synthesis) Phase: In the "S" phase, synthesis of DNA occurs with precise duplication of chromosomes. This permits the cell to divide into two daughter cells, each with a complete copy of DNA.

G2 (Gap2) Phase: In the Gap2 phase, the cell again undergoes growth and protein synthesis so that it will have enough protein for two cells.

M (Mitosis) Phase: In the mitosis phase, the enlarged parent cell divides to produce daughter cells.¹⁰⁴

With the completion of the M phase, cells which will continue to divide return to G1 and the cycle begins again.¹⁰⁵ Most critical for an understanding of cancer development is the fact that the cycle of cell division is marked by periods of inactivity or checkpoints at which a cell either repairs damaged genes, or sends a signal that activates programmed cell death (apoptosis). The principal checkpoint appears at the G1/S boundary.¹⁰⁶ A second such checkpoint or gateway which is less understood, occurs at the G2/M boundary.¹⁰⁷

Different types of cells vary widely in the rate at which they divide.¹⁰⁸ Epithelial cells, like those of the skin or which line the colon, and red blood cells produced by the bone marrow divide and replicate with high frequency, once every two or three days.¹⁰⁹ Others, such as nerve cells and muscle cells, generally do not divide further in mature humans. Liver cells retain the ability to divide, but typically do not do so unless necessary to repair a wound.¹¹⁰

D. Genetic Mutation

Independent of external stimuli, cells do not always make perfect copies of their DNA,¹¹¹ and, as noted, DNA can also be

104. *Id.* at 17-22.

105. See ALISON & SARRAF, *supra* note 4, at 134.

106. *See id.*

107. See ROSS, *supra* note 19, at 23.

108. See IAN F. TANNOCK & RICHARD HILL, *THE BASIC SCIENCE OF ONCOLOGY* 161 (3d ed. 1998).

109. See WEINBERG, *supra* note 5, at 80.

110. *See id.* at 60.

111. See ROSS, *supra* note 19, at 22; WEINBERG, *supra* note 5, at 59.

damaged as a result of outside factors.¹¹² Such imperfections are corrected by the cell itself.¹¹³ But if the damage to a cell's DNA is not repaired (or the cell itself has not been destroyed through apoptosis), a cell that contains a genetic mutation will pass that mutation on to its daughter cell through cell division that occurs as part of the cell cycle.¹¹⁴ Not all mutations to genes are harmful. Indeed, genetic mutation (in germline cells) lies at the heart of the process of natural selection and evolution. There are good mutations as well as bad mutations, but most mutations are neutral.¹¹⁵

Genetic mutations frequently occur spontaneously.¹¹⁶ The majority of spontaneous mutations occur due to the nature of the DNA and the cell's metabolism. The cell's normal energy metabolism releases millions of highly reactive molecular by-products every day. Many of these are oxidants, "free radicals," which have unpaired, highly reactive electrons.¹¹⁷ Like environmental toxins these indigenous molecules can chemically alter molecules in the cell including the molecules that make up the cell's DNA.¹¹⁸ "Immediately after DNA polymerase—the enzyme responsible for DNA replication—has copied a stretch of DNA, as many as one in every thousand bases of the newly made DNA strand may be incorrect, having been mistakenly inserted by the polymerase."¹¹⁹ Scientists estimate that about 600,000 of the three to six billion base pairs will have been erroneously copied during a single round of DNA synthesis.¹²⁰

Regardless of their origin, i.e., viral, environmental, hereditary, or spontaneous, mutations to certain vital genes which help regulate cell growth and repair are more important than damage to other genes within a cell. These critically important growth and repair genes are referred to as oncogenes, tumor suppressor genes, and DNA repair genes. Before examining how changes to the cell's key growth and repair genes affect the development of cancer, however, it is

112. See discussion *supra* notes 47-52 and accompanying text.

113. See WEINBERG, *supra* note 5, at 257.

114. See *id.* at 59.

115. See ROSS, *supra* note 19, at 7.

116. See WEINBERG, *supra* note 5, at 59.

117. See *id.* at 88.

118. See *id.*

119. *Id.* at 89.

120. See ROSS, *supra* note 19, at 22.

useful to step back and assess the significance of two of the factors just discussed—the *source* of the mutation, and the *size* of the gene that is mutated.

First, it is noteworthy that the body itself spontaneously causes genetic mutations. Though most of the cell's copying mistakes are corrected and not perpetuated in the DNA of descendent cells, the fact that these errors occur spontaneously changes the backdrop against which any classification of "injury" must be read. The human body is not a perfect system that occasionally receives an insult from an external source, but a complex and fluid balancing act that is always in the process of deterioration and repair. In this context, courts that base the continuous trigger on actual injury in the policy period should be careful about seizing a single mutation of a minute piece of genetic information and labeling it as an "injury" or evidence of "continuing" harm. To do so risks turning what is, in essence, an innocuous and normal biological process into an injurious event that carries major legal significance.

Second, as noted, "injury" is also a problematic term to describe minute changes to the infinitesimally tiny nucleotides whose deletion or subtle sequential rearrangement can constitute a genetic mutation. There are between 70,000 and 100,000 genes in each cell and each gene in turn is comprised of different sequences of four nitrogenous bases¹²¹ called nucleotides that form DNA's double helix. Each cell thus contains billions of bases, i.e., specific units of the nucleotides C, G, T, or A, arranged in different sequences. For example, though some base sequences in genes are longer and some are shorter, the substitution of a single base of guanine by thymine, in a gene that has over 5,000 bases in its sequence, is enough to constitute what is termed a "point mutation."¹²² These extremely subtle genetic changes can—if many other internal and external events occur and many other systems fail—be part of a process that yields dramatic consequences decades later. But it is misleading to identify a point mutation that occurs in 1965 by the same term used to describe a metastatic tumor that appears thirty-five years later in the year 2000. Indeed, if one does use that term to describe the entirety of the process then, in effect, one is

121. Adenine, Thymine, Cytosine, and Guanine.

122. See WEINBERG, *supra* note 5, at 42.

describing virtually all humans as being in a constant state of injury.

E. *Mutations in Key Growth Control and Repair Genes*

Within the genome are certain key genes whose normal function is to tell a cell when to divide, and/or when and how genes within the cell must be repaired. These are called oncogenes, tumor suppressor genes, and repair genes.

1. *Oncogenes*

Oncogenes are mutated forms of genes that are referred to as proto-oncogenes which, in healthy cells, encourage and promote normal growth and cell division.¹²³ Proto-oncogenes encourage and promote the normal growth and division of cells. When proto-oncogenes mutate to become carcinogenic oncogenes, they stimulate excessive cell multiplication.¹²⁴

A cell communicates with the cells of surrounding tissue through receptors on the surface of the cell. The communication goes both ways, i.e., these receptors relay signals from outside into the cell nucleus and from inside the cell to other cells.¹²⁵ Normally, proto-oncogenes provide a code for cellular proteins that allow them to relay signals to a cell's nucleus, stimulating growth. The cellular proteins used in the relay system are responding to signals from other neighboring cells.¹²⁶ This signaling process involves a series of steps in which information encoded in proteins is passed along in a chain-like "bucket brigade" from the exterior cell membrane to the cell's inner core.¹²⁷ The signaling process ends in the nucleus with the activation of transcription factors that are sent to the promoter regions of genes which trigger cell division.¹²⁸

During the life of a cell, proto-oncogenes along the message pathway may mutate. When mutated, the proto-oncogenes become oncogenes that keep the path continuously active when it should be quiescent.¹²⁹ Unlike proto-oncogenes,

123. See ROSS, *supra* note 19, at 32.

124. See VOGELSTEIN & KINZLER, *supra* note 1, at 205.

125. See SCI. AM., *supra* note 58, at 4.

126. See WEINBERG, *supra* note 5, at 97.

127. See SCI. AM., *supra* note 58, at 4.

128. See ROSS, *supra* note 19, at 32-33.

129. See VOGELSTEIN & KINZLER, *supra* note 1, at 205.

oncogenes thus divorce cell proliferation from the complex set of growth and anti-growth signals received from neighboring cells. They make a cell's replication mechanism responsive to its own internally generated and ongoing growth stimulation signals.¹³⁰ Mutations that turn proto-oncogenes into oncogenes are rare, occurring in fewer than one-in-a-million cell divisions.¹³¹ When this one-in-a-million risk materializes, however, the oncogenes behave like a stuck accelerator on a car, constantly urging it forward.¹³² "There are presently nearly 200 known oncogenes that, under certain conditions, can contribute to the release of cells from the normal controls of proliferation, death, migration and adhesion to cause neoplastic transformation."¹³³

2. *Tumor Suppressor Genes*

Unlike proto-oncogenes which stimulate the cell cycle, tumor suppressor genes normally inhibit the cycle of cell growth and division.¹³⁴ Like oncogenes, the tumor suppressor genes operate at many sites from outside the cell to the cell surface to the nucleus. In normal cells, tumor suppressor genes function to stop or to slow the cell cycle until damaged or incorrectly copied DNA can be repaired.¹³⁵ Other tumor suppressor genes help trigger cell death if it is sensed that the DNA damage is too extreme to be repaired.¹³⁶

Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals.¹³⁷ This removes the brakes from the cell cycle and results in a higher rate of cellular division. Though estimates are imprecise, there are thought to be as many as three to four dozen distinct tumor suppressor genes.¹³⁸

The most widely known tumor suppressor gene is p53. The p53 tumor suppressor gene is involved in a wide range of

130. See WEINBERG, *supra* note 5, at 107.

131. See *id.* at 56.

132. See WEINBERG, *supra* note 5, at 251; ALISON & SARRAF, *supra* note 4, at 65.

133. ROBIN HESKETH, *THE ONCOGENE AND TUMOUR SUPPRESSOR GENE FACTS BOOK 5* (2d ed. 1997).

134. See ROSS, *supra* note 19, at 45.

135. See BISHOP & WEINBERG, *supra* note 3, at 133.

136. See TANNOCK & HILL, *supra* note 108, at 107.

137. See WEINBERG, *supra* note 5, at 68-69.

138. See *id.* at 77.

tumors.¹³⁹ In fact, more than fifty percent of cancerous cells lack a functional p53 protein.¹⁴⁰ Also widely known are BRCA1 and BRCA2, tumor suppressor genes which are involved in ovarian and breast cancer.¹⁴¹

The deactivation of a tumor suppressor gene is even less likely to occur than the mutation of a proto-oncogene—a one-in-a-billion chance.¹⁴² This is because tumor suppressor genes, like almost all genes in the body, are present in two copies, one from the mother and one from the father. The loss of one tumor suppressor gene will not cause problems—the remaining copy is usually sufficient by itself to perform the tumor suppressor function.¹⁴³ In about one in a thousand cases, however, both versions of the same gene (heterozygosity) are lost because the gene sequence present on one chromosome is replaced by the corresponding sequence carried by its partner.¹⁴⁴ When this happens after one of the tumor suppressor genes has been mutated, the still intact or proper copy of the tumor suppressor gene may be lost, i.e., replaced by the duplicated copy of the mutated version of the gene. Thus, the direct mutation of a tumor suppressor gene, which occurs once per every million cell divisions, must be multiplied by the one in one thousand frequency of loss of heterozygosity, resulting in the loss of a functional tumor suppressor gene only once per every billion cell divisions.¹⁴⁵

3. *DNA Repair Genes*

Along with proto-oncogenes and tumor suppressor genes, DNA repair genes are believed to be key genes in causing cancer. These are genes that in ordinary operation help ensure that each strand of genetic information is accurately copied during the course of cell division. The cellular mechanisms charged with repairing DNA consist of a large group of proteins, some of which recognize damaged DNA segments, others which cut them out, and still others which substitute the excised segments with new ones that restore

139. See ALISON & SARRAF, *supra* note 4, at 183.

140. See WEINBERG, *supra* note 5, at 77.

141. See SCI. AM., *supra* note 58, at 13.

142. See WEINBERG, *supra* note 5, at 76.

143. See ALISON & SARRAF, *supra* note 4, at 74.

144. See ROSS, *supra* note 19, at 48; WEINBERG, *supra* note 5, at 76.

145. See WEINBERG, *supra* note 5, at 76.

the proper base sequence.¹⁴⁶ Because DNA replication in cell division is prone to error, it is critical that the repair genes properly perform their tasks. Mutations in DNA repair genes lead to an increase in the frequency of other mutations.¹⁴⁷

F. *Cancer Promoters*

In addition to endogenous or exogenous mutagens that cause genetic mutations there are other agents called "promoters" which contribute to the development of cancer by speeding up the cell cycle. Substances such as alcohol, asbestos, and estrogen are relatively weak mutagens themselves, but contribute to or promote the development of cancer in various ways.¹⁴⁸ Other toxic agents, like cigarette smoke, contain chemicals which both *initiate* the process by causing mutation and *promote* it as well.¹⁴⁹ Some such promoters simply cause the DNA in cells to be copied more frequently, thus creating increased possibilities of a mistake.

Estrogen, for example, is a fully natural hormone that drives proliferation of cells lining the milk ducts during the menstrual cycle and pregnancy.¹⁵⁰ The monthly replication of these cells is followed by their death. Women of the present era tend to menstruate earlier, bear fewer children, bear them later in life, and breast-feed for shorter periods of time. These facts all combine to cause more menstrual cycles, more estrogen production and more rounds of cell division. Scientists now believe that estrogen, through this mechanism, has become a promoter of breast cancer.¹⁵¹

Similarly, the hepatitis B virus may promote the development of liver cancer even though it does not have any direct mutagenic effect on DNA. Although it does not directly damage DNA, the virus kills off cells in the livers of infected persons.¹⁵² Normal liver cells rarely divide and replicate. Livers infected with the hepatitis B virus, however, are constantly replacing dead cells. The higher rate of cell division leads to a greater frequency of miscopied and/or unrepaired liver cells, and ultimately to an increased risk of

146. See TANNOCK & HILL, *supra* note 108, at 58-66.

147. See WEINBERG, *supra* note 5, at 88.

148. See *id.* at 60.

149. See ROSS, *supra* note 19, at 60.

150. See WEINBERG, *supra* note 5, at 60.

151. See *id.* at 61.

152. See *id.* at 60.

liver cancer.¹⁵³

Even after mutations to key growth or repair genes have occurred, tumor development is far from assured. As discussed below, other genetic mechanisms trigger cell death and thus help check uncontrolled cell growth. Before reviewing these mechanisms at work, however, it is useful once again to observe the poor fit between normal definitions of injury and the more fluid, dynamic character of cancer development. As noted, the terms “injury” and “disease” seem inapt because genetic mutations are infinitesimally minute, can occur spontaneously during cell replication, and, to one degree or another, affect the entire population all of the time. But these are only some of the definitional problems. The relative risks and probabilities that any such mutation will develop into cancer must also be taken into account.

Damage to DNA and genetic mutation occurs almost constantly in the human body—and almost never results in cancer. The risk of a key mutation to any particular cell is very low, and the risk that any particular genetic mutation will be part of a sequence of important mutations that leads to cancer is extremely unlikely. As discussed above, a mutation that activates an oncogene occurs only once per every million cell divisions. The chance for mutating a tumor suppressor gene such that it becomes non-functional is one-in-a-billion. Even when such a mutation does occur, it usually does not otherwise lead to cancer. Between four to seven such events or mutations to a single cell are necessary before a malignant tumor will commence—and even then, as will be discussed below, the cell must avoid apoptosis, senescence, crisis, and somehow metastasize before human fatality is likely to occur. There may be long intervals between key mutations. The body produces ten million billion cells over the course of an average life span.¹⁵⁴ There is a fatal malignancy that develops in only about one in every 100 million billion cell divisions.¹⁵⁵

On the other hand, within the thirty trillion cells of the body, genetic damage is frequently occurring and almost as frequently being repaired. As the discussion of oncogenes, tumor suppressor genes, and DNA repair genes indicates, the

153. *See id.*

154. *See id.* at 142.

155. *See id.*

body is in a constant state of error and self-correction. As Professor Weinberg has explained, "So the rock-solid stability of the cell's genetic data base is a mirage. The constancy of our genome is the result of a high-wire balancing act, a permanent struggle in which an ever-vigilant repair apparatus continually fights off genetic chaos."¹⁵⁶

Advocates of a continuous trigger, when confronted with (1) almost immeasurably small genetic alterations, which (2) occur spontaneously as well as a result of exogenous factors, and which (3) almost never lead to full-blown cancer, will argue that none of this is relevant. Adopting what is referred to as a "retrospective analysis," they contend that as long as it is apparent through hindsight that the particular genetic mutation did, in fact, appear somewhere in the chain of events that eventually resulted in cancer, the term injury is proper. As discussed later, however, such a retrospective analysis can be more misleading than it is informative in the context of cancer. Indeed, though a particular mutation, when and if it occurs, might in some sense be considered "injurious" if it is traceable to an external source (as opposed to a hereditary or endogenous cause), it is inadvisable to identify the very process of being alive—this "high wire balancing act" in which mutation and repair are always ongoing—as a state of injury, sickness, or disease.

G. *Methods of Cell Death*

In order to advance along the path to cancer, cells must not just sustain mutations to the genes that (1) stimulate and (2) inhibit cell growth and (3) influence DNA repair and/or (4) be influenced by "promoters" that encourage the cell to divide more frequently. They must also sustain mutations to genes that are programmed to cause the death of the cell upon the cell's perception of excessive growth, damage, or mutation. There are at least three separate mechanisms of cell death that must be overcome if cancer is to occur: apoptosis, senescence, and crisis.

1. *Apoptosis*

Apoptosis is programmed cell death. It is a self-destruct mechanism that triggers the death of a cell when genes

156. WEINBERG, *supra* note 5, at 90.

encoded to receive such information perceive a defect, such as the signal of a mutant protein product from an oncogene.¹⁵⁷ In some manner that is still unclear, cells sense when they have sustained serious damage to their DNA.¹⁵⁸ Rather than attempting to repair such serious damage, they are wired to commit suicide. Even very subtle abnormalities in the internal growth regulating circuitry of cells can trigger the programmed death of a cell.¹⁵⁹ For example, the introduction of a “myc” oncogene into a normal cell seems not only to stimulate excessive growth,¹⁶⁰ but to cause a signaling imbalance that provokes many cells to trigger their apoptotic death program.¹⁶¹

One of the reasons that damage to the p53 tumor suppressor gene is so serious is that the p53 gene plays a role not just in slowing down the cell cycle so that DNA repair genes can do their work, but it is also responsible for transmitting messages to those genes which trigger programmed cell death.¹⁶² Thus, p53 tumor suppressor genes have multiple tasks. When relatively minor DNA damage is sustained, the p53 tumor suppressor gene will temporarily halt the cell’s growth so that repair may be effectuated. On the other hand, where the damage is more severe and exceeds the capabilities of the DNA repair machinery, the p53 protein will determine whether apoptosis is the appropriate response.¹⁶³

2. *Senescence*

A second back-up system comes into play for cells with genetic mutations that successfully evade apoptosis. Normal cells are incapable of further reproducing themselves after fifty or sixty replications.¹⁶⁴ This is because the chromosomal tips, called telomeres, which contain 1,000 or more base repeats of the TTAGGC sequence necessary for cell

157. See ALISON & SARRAF, *supra* note 4, at 171.

158. See WEINBERG, *supra* note 5, at 123.

159. See *id.* at 122.

160. See *id.* at 107-08.

161. See ALISON & SARRAF, *supra* note 4, at 183-84.

162. See *id.*

163. See *id.* (“The function of p53 has been likened to that of a molecular policeman or guardian of the genome; when DNA is damaged, p53 accumulates and switches off replication to allow time for DNA repair. . . . If repair fails, p53 may trigger apoptosis.”)

164. See SCI. AM., *supra* note 58, at 10.

replication, are shortened by dozens of nucleotide bases each time a cell divides.¹⁶⁵ After forty or fifty cell doublings, the telomeres become worn down and shortened so that they lose their ability to protect the tips of the cells' chromosomes. The chromosomes consequently fuse end to end creating genetic disarray that causes cells to stop growing and eventually die. This telomeric collapse is called senescence and normally prevents cells from excessive proliferation.¹⁶⁶

3. *Crisis*

Cells whose p53 tumor suppressor genes are defective, however, may not only avoid apoptosis, but senescence as well. They are sometimes able to continue growing in spite of the telomeric shrinkage and multiply for another ten or twenty cell generations. Even these cells, however, usually die by entering a phase known as crisis.¹⁶⁷ In this phase, a second internal cellular alarm is sounded, apparently triggered by telomeres that have continued to shorten and reach a critically short size. Cells of this type suddenly die in large numbers during the crisis phase.¹⁶⁸

H. *Telomerase and Immortality*

An extremely rare cell, however, will evade apoptosis, senescence, and crisis, and go on to live as an "immortal cell" that continues to replicate and proliferate indefinitely. Cells of this type survive by the activation of a gene that is coded for the production of the enzyme telomerase.¹⁶⁹ This enzyme, almost entirely silent in healthy cell types (other than embryonic cells), is actively present in almost all tumor cells and systematically replaces telomeric segments that are cut away from the chromosomal ends during the normal cell cycle.¹⁷⁰ Thus, it maintains the integrity of the telomeres and allows these cells to replicate endlessly.¹⁷¹

Even after surviving or evading the various mechanisms of cell death, there remain significant obstacles to tumor

165. See WEINBERG, *supra* note 5, at 116.

166. See TANNOCK & HILL, *supra* note 108, at 145.

167. See SCI. AM., *supra* note 58, at 10.

168. See WEINBERG, *supra* note 5, at 129.

169. See ROSS, *supra* note 19, at 147.

170. See SCI. AM., *supra* note 58, at 11.

171. See WEINBERG, *supra* note 5, at 116.

development. The fact of cell death and the multiple ways it can occur, however, points up further inadequacies in the use of the term "continuous injury" to describe all phases leading up to the development of cancer. Although genetic mutations in any given cell are commonplace, mutations that impact key growth and repair genes are rare. Even after a cell has sustained a mutation to one of its critical genes, it is possible that the cell or group of cells with the mutant genes will die. It may take a long time for a cell with one mutation to receive a second or a third key mutagenic event. Though it may be possible, in some sense, to describe the mutation itself as "injury," it is apparent that the lengthy period of time *in between* significant mutations should not be so described.

I. *Further Obstacles to Tumor Development*

1. *Angiogenesis*

Even if a cell has survived after damage to its proto-oncogenes, tumor suppressor genes, and DNA repair mechanism, and somehow evaded apoptosis, senescence, and crisis, very significant hurdles remain before the mutant cell can proliferate to any significant degree. First, incipient tumors require constant nourishment and oxygen. As long as the tumor cells remain less than a millimeter in diameter, they can depend on the process of diffusion¹⁷² to provide nourishment with oxygen and to rid the cells of carbon dioxide and the waste products of their metabolism.¹⁷³

At the size of one millimeter, however, the process of diffusion is inadequate to the demands of growth.¹⁷⁴ Before long, cells within the cluster become starved or begin to choke on their own waste materials. These cells become oxygen-starved and die from a p53-mediated form of apoptosis. At some point, the death rate of these cells from asphyxiation and metabolic poisoning begins to approach the rate at which these cells can regenerate themselves.¹⁷⁵ Any gains made

172. Diffusion is the movement of a substance from an area of high concentration to an area of low concentration. In cells, the movement and exchange gases, nutrients, and water through the cell membrane is accomplished by this process.

173. See ROSS, *supra* note 19, at 63.

174. See WEINBERG, *supra* note 5, at 145.

175. See ALISON & SARRAF, *supra* note 4, at 186.

through cell proliferation are neutralized by attrition, and so the size of this tumor cell clump remains constant. If cancerous tumors did not grow larger than the size of a pinhead, they would not present a medical problem.¹⁷⁶ Some clusters of tumor cells may remain in this static, microscopic state for years and maybe even decades.¹⁷⁷

In order to grow beyond the size of a millimeter, the incipient tumor must obtain its own direct access to the blood supply.¹⁷⁸ This process, called angiogenesis, involves the construction of blood vessels and occurs when some cells in the tumor cluster mimic the behavior of the normal cells around them. The cells also secrete growth factors that attract endothelial cells from nearby tissues, inducing them to multiply and to grow capillaries into the clump of cluster cells.¹⁷⁹ At this point, the tumor can begin to grow explosively.¹⁸⁰ It remains unclear at this time, however, how tumor cells acquire the ability to generate these in-growing blood vessels.

2. *Metastasis*

Even where tumors develop their own blood supply through the process of angiogenesis, they will rarely become lethal unless they metastasize and colonize other sites in the body. Of those patients who die from cancer, fewer than ten percent succumb from tumors that continue to grow at their point of origin.¹⁸¹ In the great majority of cases the killers are metastases—colonies of cancer cells that have left the site of the original, primary tumor and have settled elsewhere in the body.¹⁸²

The process of metastasis is as yet little understood.¹⁸³ To metastasize, however, major hurdles must be overcome. First, cells within the primary tumor mass must escape the barrier that surrounds their growth. Epithelial cell layers are underlaid by a structural meshwork of proteins called the

176. See ROSS, *supra* note 19, at 63.

177. See WEINBERG, *supra* note 5, at 144.

178. See *id.* at 145.

179. See SCI. AM., *supra* note 58, at 124; BISHOP & WEINBERG, *supra* note 3, at 196-99.

180. See WEINBERG, *supra* note 5, at 145.

181. See *id.* at 146.

182. See ALISON & SARRAF, *supra* note 4, at 110.

183. See WEINBERG, *supra* note 5, at 149.

“basement membrane” that separates the epithelium from connective tissue and circulation.¹⁸⁴ An intact basement membrane is usually impenetrable to cells, and any invasion through it depends on the ability of cancer cells to release proteases, enzymes specialized for breaking protein chains of the basement membrane into tiny fragments.¹⁸⁵ Second, if this membrane is breached, it may give tumor cells access to blood vessels or the lymphatic system.¹⁸⁶ In either case, individual cells or small clumps of cells may break off from the principal tumor mass riding through these systems to more distant sites.¹⁸⁷

Yet even when cancer cells do get into circulation, the formation of secondary tumors is unlikely. The circulating cell must attach to the inner lining of a blood vessel, cross through it, pass through the basement membrane at the new location, and then invade the tissue beyond and begin multiplying. “The journey through the blood vascular system is extremely hazardous as tumor cells get jostled in a series of high speed collisions with the vessel walls and each other; only a minority of blood borne cancer cells seem to survive this traumatic experience.”¹⁸⁸ Indeed, probably fewer than one in 10,000 of the cancer cells that reach circulation survive to form a new tumor at a distant site.¹⁸⁹

Once the tumor cells reach a new site, they encounter further problems. Cancer cells follow the pathways of the circulatory system and tend to lodge in the first capillary network they encounter downstream.¹⁹⁰ Not all such sites, however, are receptive to transplanted cell colonies. Cells contain internal regulatory mechanisms that make them compatible or incompatible with neighboring cells. These mechanisms, somewhat like telephone area codes, help prohibit a cell from leaving its normal home and establishing a colony in an incompatible “area code.”¹⁹¹ Other researchers explain this phenomenon by a seed and soil analogy “likening cancer cells to ‘seeds,’ which after being scattered on the

184. See ROSS, *supra* note 19, at 64.

185. See BISHOP & WEINBERG, *supra* note 3, at 199-200.

186. See TANNOCK & HILL, *supra* note 108, at 221-24.

187. See BISHOP & WEINBERG, *supra* note 3, at 201.

188. ALISON & SARRAF, *supra* note 4, at 110.

189. See SCI. AM., *supra* note 58, at 19.

190. See ALISON & SARRAF, *supra* note 4, at 111.

191. See SCI. AM., *supra* note 58, at 17.

'wind,' grow only in sites – ('soil') that are congenial to their survival and further growth."¹⁹²

At this time, less is known about the process of metastasis than is currently known about the process of tumor formation. Theoretically, interactions between tumor cells and the endothelial cells of the capillaries where the movement of the tumor cell is arrested, initiate signaling pathways that promote metastasis by inducing expression of genes, which helps the colonizing tumor cell attach and adhere to the new host tissue.¹⁹³

The complex hurdles a mass of malignant cells must overcome in creating its own blood supply and, then after further maturation, in forming new tumors at other sites, are significant for coverage analysis. If there is this much risk and uncertainty to the development of cancer *after* a tumor has formed, then courts should be doubly cautious about labeling *pre-cancerous* groups of cells and/or initial genetic mutations as injury or disease.

IV. IMPLICATIONS FOR TRIGGER ANALYSIS

A. *The Process of Cancer Development Does Not Constitute a Continuous Injury*

Even this brief outline of cancer development makes it apparent that, as the district court stated in *Stonewall*,¹⁹⁴ it is difficult to fit complex medical phenomena like "cancer" into terms of ordinary language like "injury." As another cancer researcher has likewise commented, "cancer is more complex than an all-or-none phenomenon," and "a tumor cannot be simply classified as either benign or malignant."¹⁹⁵ Despite the continuous thread that leads from the first critical genetic mutation to a malignant tumor, there are numerous and significant aspects to the process of cancer development that do not match well with traditional definitions of injury, sickness, or disease. These factors have been noted in the foregoing discussion, but it is useful to review them again here.

192. ALISON & SARRAF, *supra* note 4, at 112.

193. See TANNOCK & HILL, *supra* note 108, at 230-31.

194. *Stonewall Ins. Co. v. Asbestos Claims Management Corp.*, No. 86 Civ. 9671(JSM), 1998 WL 405047, at *1 (S.D.N.Y. July 17, 1998).

195. ROSS, *supra* note 19, at 70-71.

1. *The Processes Underlying Cancer Development Are Too Common to Be Called "Injury"*

Somewhere between thirty-three and forty percent of all people will contract cancer at some point in their lives. Although most people will not get cancer until their seventies, use of the continuous injury trigger would brand such persons as "injured" from the time of childhood until death. More significantly, even people who do not ever contract cancer during their lifetime always have cells bearing genetic mutations, some of which appear in critical oncogenes, tumor suppressor genes, and DNA repair genes. In the context of multistage development of cancer,¹⁹⁶ cells are frequently "initiated" with initial genetic alterations or mutations. As a leading cancer researcher has observed:

However, studies of DNA structural changes in liver following single very low initiating doses of carcinogens showed considerable DNA fragmentation . . . indicating that DNA damage and mutations were extensive even at subcarcinogenic doses. On the basis of the known mutation-inducing capability of such agents, many mutations are induced in cells and numerous initiated cells are likely to be induced by carcinogens even at the low doses to which humans are usually exposed. *Thus it is very likely that adult organisms possess numerous initiated cells in most organs, making initiation an extremely common event that occurs frequently both spontaneously and by induction, experimentally, or otherwise, in animals as well as humans.*¹⁹⁷

Therefore, according to the view that brands the mere initiation of a DNA mutation in a cell as injury, everyone is injured all the time.

2. *There Are "Spontaneous" Mutations that Can Lead to Cancer*

A genetic mutation does not result solely from external stimuli. The body's own metabolism and the nature of DNA itself cause genetic mutations.¹⁹⁸ As many as twenty-five percent of all cancers would occur regardless of the adverse

196. See *supra* note 3.

197. Pitot, *supra* note 21, at 1613 (emphasis added).

198. See *supra* notes 81-82.

effects of certain lifestyle choices and environmental factors.¹⁹⁹ Because the body itself produces genetic mutations, it is more difficult to automatically brand mutation abnormal and injurious.

3. *Genetic Mutations Are Infinitesimally Minute*

Minor alterations in any metabolic process can ultimately lead to dramatic adverse consequences. It is odd, however, to refer to the almost immeasurably tiny alteration of a single gene or base in a single cell, by itself, as injury. This is especially so when it is considered that these tiny alterations can occur naturally within the body, and are occurring all the time to all people, but that it is extremely rare that any particular such alteration will lead to cancer.

4. *The Chance of Developing Cancer from Any Particular Genetic Mutation Is Extremely Low*

The chance that a proto-oncogene will mutate into a potentially cancer-producing oncogene is one in one million.²⁰⁰ The chance that a cell will lose an effective tumor suppressor gene is one in one billion.²⁰¹ Even if such mutations occur, it is likely that the cell will die by means of apoptosis, senescence, and crisis. Thus, "cancer is usually held at bay because it depends on a convergence of rare events that are unlikely to occur in an average human lifespan."²⁰²

In the tort context, before permitting parties to sue for fear of cancer, courts like the California Supreme Court have required a showing that it is more probable than not that cancer would result because of a given exposure.²⁰³ Although different definitions of injury apply in different legal contexts, it is nonetheless anomalous to require a demonstration that cancer is *probable* in order to affix liability in the tort system, yet to brand a genetic mutation as "injury" in the insurance context, when the possibility that that mutation will lead to cancer is negligible at best, is common.

199. See *supra* notes 81-82.

200. See *supra* note 131.

201. See WEINBERG, *supra* note 5, at 153.

202. *Id.* at 143.

203. See *Potter v. Firestone Tire & Rubber Co.*, 6 Cal. 4th 965 (1993).

5. *There Is No New Injury in the Interval Between Mutations*

Even if one were to assume that the term "injury" could usefully apply to each of the four to seven key genetic mutations that lead to the development of a malignant tumor, there are long intervals between such mutations.

Following each critical mutation, the descendants of the recently mutated cell would need to multiply into a flock of a million or more before the next one-in-a-million mutation became likely in one of its descendants. This expansion in cell population might take several years to a decade, explaining the long intervals between the successive steps in the process of tumor formation.²⁰⁴

It is true that a genetic mutation may carry with it a tendency to make a cell replicate more frequently, thus elevating the risk that the cell will acquire a second critical mutation simply as a result of the cell's own tendency to mis-copy its genome in the course of cell replication. Yet, this ill effect is part and parcel of the injury associated with the original mutation itself and not a further and additional injury.

Taken by themselves, perhaps no single one of these factors would dictate the rejection of the "continuous injury" designation for cancer. Taken collectively, however, they acquire a weight and force that cannot be ignored. Though these factors do not necessarily point to the "correct" trigger, they strongly suggest that it is not possible to justify a continuous injury trigger in the latent phases of cancer cases where the toxic agent is not absorbed and retained in the body to cause further mutation.

B. *Problems with Arguments in Favor of Continuous Trigger*

Despite the problems in applying a continuous trigger to cancer cases, it is likely that advocates of this coverage theory will argue in favor of its use in all cancer cases on three separate grounds. They will likely claim (1) that each replication of a damaged cell is a "new" injury, (2) that the proliferation of damaged cells is a "new injury," and (3) that under a "retrospective analysis," it is plain from hindsight that even the initial genetic mutation constituted injury

204. WEINBERG, *supra* note 5, at 56.

because in the end, cancer did, in fact, develop. While these arguments are interesting, none of them justifies the conclusion that "continuous injury" accurately describes all phases of cancer development.

1. *The Argument that Cell Replication Is New Injury*

In the context of asbestos-related cancers, at least one court has held that "[e]ach replication of a damaged cell constitutes a new injury."²⁰⁵ It is unclear to what extent this statement was intended by the court to have meaning outside the context of asbestos-related diseases where the carcinogen remains in the body. It is likely that the same argument will be made in other cancer cases where this is not the case. In other cancer cases, however, the argument seems wrong.

If it is proper to characterize the original mutation itself as "injury," there is no "new" injury to the cell during the period between the first and second key mutations. During this interval, the original injury persists and is replicated. Similarly, if a cell accumulates two key genetic mutations, and the second mutation is itself viewed as another "injury," there would not be any "new" injury after the occurrence of the second key genetic mutation until such time as a third critical mutation might occur. The mere persistence of a mutation through its replication in daughter cells should not be viewed as new injury for purposes of coverage analysis.

The fact that mutations to the genes which regulate a cell's replication and repair mechanisms persist in the daughter cells and help increase the chance for additional mutations does not necessarily make such persistence "new" injury. This elevated risk is itself not "new injury" but may be viewed as simply a consequence of the original mutation, or the preceding accumulation of them. For example, a mutation that affects one of the cell's proto-oncogenes may increase the rate of cell replication and make additional mutations more likely. But until the additional mutation occurs—if it ever does—this increased rate of cell replication itself should properly be viewed as the persistence of the original mutation to the proto-oncogene that has transformed it into a mutant oncogene.

205. *Stonewall Ins. Co. v. Asbestos Claims Management Corp.*, No. 86 Civ. 9671(JSM), 1998 WL 405047, at *2 (S.D.N.Y. July 17, 1998).

2. *The Argument that Cell Proliferation Is a New Injury*

A variation of the first argument stems from the higher rate of cell replication that occurs in cells that have sustained mutations to critical growth and repair genes. Due to this higher rate of replication, it is theorized that cells bearing a particular mutation will increase in number more than they would have if there had not been the mutation. With this increase in number comes the elevated risk that one among this greater number of cells will sustain a second mutation. Again, the district court in the *Stonewall* case listed this factor among those which persuaded it that there was "injury in fact" during the latency period prior to the appearance of asbestos-related cancer. "The medical testimony shows that asbestos can contribute to the cancer process . . . [by] increas[ing] the rate of proliferation in already mutated cells causing the body to have an increased number of such cells, thereby increasing the risk of further mutations"²⁰⁶

Several points are pertinent here. First, the exact extent of increased cell proliferation is unknown and, in any given case, likely to be minimal. While it is believed that the genetically altered cell "enjoys a proliferative advantage over its normal neighbors,"²⁰⁷ this fact alone should hardly be determinative. The cell "circuitry is configured to resist destabilization by single malfunctioning components. Thus, the activation of an oncogene or the deactivation of a tumor suppressor gene will often have only minimal effects on the proliferation of a cell."²⁰⁸ Cell proliferation, even in mutated cells, is kept in check by the death of cells through apoptosis, senescence, crisis, and anoxia. In most cases, these processes of cell death either keep in check or cancel entirely this increased number of cells. This is why, even when such groups of cells form a tiny tumor, the overall size "may remain . . . static . . . for years, possibly even decades."²⁰⁹ Indeed, if this were not the case, the multi-step process of cancer that unfolds over three to five decades would be telescoped into a period of eight to ten years. The fact that this kind of telescoping does *not* occur indicates the extremely subtle and marginal character of any increase in the overall

206. *Id.*

207. ALISON & SARRAF, *supra* note 4, at 37.

208. WEINBERG, *supra* note 5, at 142.

209. *Id.* at 144.

number of cells that occurs during the interval between mutations.

Second, as noted earlier, cells may proliferate as a result of spontaneous mutations. These mutations may involve infinitesimally minute alterations of nucleotides. And such mutation and proliferation are an ongoing process in all people at all times. The argument thus still involves describing infinitesimally tiny changes that are ongoing at all times in all people as "injury."

Third, in light of these realities, the tendency of mutated cells to increase their number is meaningful *only* if it ultimately leads to cancer. This eventuality is both unknown and highly unlikely through most of the course of cancer development. Thus, this is a factor that acquires meaning only to the extent that one employs a retrospective analysis. As discussed below, however, the retrospective analysis itself is flawed.

3. *The Argument that Under a Retrospective Analysis, Hindsight Permits a Court to Conclude that Even the First Genetic Mutation Was Destined to Lead to Cancer*

The retrospective analysis of continuing injury was first utilized by the trial court in the Coordinated Asbestos Coverage Cases that were reviewed by the appellate court in *Armstrong World Industries v. Aetna Casualty & Surety Co.*²¹⁰ There, the insurers argued that it was improper to term subclinical changes to a person's tissue as "injury" when ninety percent of the people who sustained such subclinical changes never contracted an asbestos-related disease. In response, the court explained that it was unconcerned with the ninety percent who did not become injured. As the court of appeals later affirmed:

In the present case, the trial court necessarily took a retrospective point of view. In resolving the insurance coverage questions, the court was concerned only with individuals who have actually developed asbestos-related diseases, and for such claimants, the court found that the evidence permitted the inference that injury took place in the past: "[T]he asbestos medical evidence [establishes] *in retrospect* that undiscovered injury existed during the

210. 52 Cal. Rptr. 2d 690 (Cal. Ct. App. 1996).

asbestos exposure period and during the latency period in the absence of exposure.”²¹¹

The ineradicable presence of asbestos fibers and the ongoing exposure to asbestos in the lungs may have created an aura of inevitability about asbestos diseases once they actually developed. But the rarity and unpredictability of genetic mutations make such a retrospective analysis unpersuasive in the context of other cancers.

To classify one genetic mutation (out of thousands) that occurred in 1975 as “injury” because, with the benefit of hindsight, it was apparent in 2010 that the mutation developed into cancer is to invoke a very peculiar use of the term “injury.” It makes the occurrence of “injury” in 1975 dependent upon (a) later events (i.e., further important mutations) that were (b) not only contingent and unpredictable in 1975, but (c) highly unlikely to happen. It is additionally strange because the later mutations, if they occur, may be caused by lifestyle choices and/or by factors that are entirely unrelated to the first mutation; or, in fact, they may be spontaneous in origin and thus, relate to no outside factor at all.

The oddity of this retrospective thesis calls to mind the analysis of an appellate court in DES coverage litigation. In applying a continuous trigger in the DES context, the court in *American Home Products Corp. v. Liberty Mutual Insurance Co.*²¹² barred the application of a coverage theory proffered by one of the parties on the ground that it would reverse the normal sequence of cause and effect and, in essence, require the effect to *precede* the cause:

An effect never precedes its cause. The policies plainly give coverage for injury that occurred during the policy period and was caused by exposure to [the insured’s] products; injury occurring during the policy period could not have been caused by an exposure that occurred thereafter.²¹³

The so-called retrospective analysis, however, effectively does the same. It labels an event injurious not by virtue of its intrinsic harm or its contemporaneous appearance, but solely by virtue of contingent and unlikely events that occurred

211. *Id.* at 704 (citation omitted).

212. 748 F.2d 760 (2d Cir. 1984).

213. *Id.* at 765.

thereafter. In a real way, the retrospective analysis thus makes the cause of the "injury" in 1975 the events which post-date 1975 by many years; it is only because of these later mutagenic events that cumulatively precipitate the development of cancer, that the earlier genetic mutation earns the title of "injury." A quick example illustrates the problem.

Assume that an individual is exposed to vinyl chloride, an agent that is known to cause liver cancer,²¹⁴ for three years between 1970 and 1973. As a result of that exposure, a proto-oncogene mutates into an oncogene. Thereafter, the exposure to vinyl chloride ceases. Vinyl chloride is not maintained in the body for any length of time after termination of exposure,²¹⁵ and thus, the only residual effect from the vinyl chloride is the genetic mutation.

At another job, this individual is later exposed to a different carcinogen and sustains a second key genetic mutation to the same cell in 1980. Throughout his life, he has eaten a diet low in fruits and vegetables and has drunk more alcohol than he should have. As a result, in 1987 and 1996 respectively, he sustains a third and fourth significant mutation in the same cell. As a result of the increased cell replications due to prior mutations and his continuing exposures to a cancer promoter like alcohol, he sustains a fifth mutation in the year 2000. By the year 2002, he has been diagnosed with liver cancer. According to retrospective analysis, the "bodily injury, sickness or disease" can be said to have existed from 1970 onward, even though he did not contract cancer until the year 2000 and did not sustain the fourth and fifth mutations necessary to give rise to cancer until 1996 and 2000 respectively.

In a second example, the same individual works at the same job where he is exposed to vinyl chloride, and at the end of 1973, he ceases that work but has an oncogene activated in one of his cells. This individual, however, continues his education and becomes an accountant and is not exposed to

214. See INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 19 IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS 377-438 (1979) (This section evaluates vinyl chloride and polymers).

215. See T. GREEN & D. E. HATHWAY, *The Biological Fate in Rats of Vinyl Chloride in Relation to Its Oncogenicity*, 11 CHEMICO-BIOLOGICAL INTERACTIONS 545, 551-52 (1975).

any further carcinogens in the workplace. In addition, he exercises, eats a healthy diet, and drinks only occasionally. As a result, he sustains a second mutation to that cell as a result of spontaneous mis-copying in the course of cell division in the year 1990, but he does not contract cancer.

Although the individual in the second example had exactly the same cellular mutation as did the person in the first example in 1973 and carried that mutation with him over the next thirty years, his mutation is not deemed to be an injury. On the other hand, the individual in the first example is deemed to have been injured continuously, even though the necessary subsequent events that made the first mutation "injurious" did not occur until ten and twenty years after the first mutation. The retrospective analysis, therefore, does more than simply permit a court with the benefit of hindsight to see an injury in 1973 that was real but not apparent at the time. Instead, it is a perspective that permits later contingent events to determine and to completely recharacterize the nature of what originally happened. This kind of analysis is not simply retrospective, but transfiguring.

V. CONCLUSION: WHAT IS THE PROPER TRIGGER FOR CANCER CASES?

The foregoing analysis suggests that a continuous trigger is not appropriate in cancer cases where the toxic agent does not remain in the body—at least for courts that seek to ground the application of a continuous trigger on a finding of "continuous injury" in successive policies periods. That the processes associated with cancer development do not fit within a continuous trigger, however, does not indicate which alternative coverage triggers might apply. Several factors are important to consider in deciding which trigger applies.

A. *When the Offending Agent Remains*

Where the offending agent remains in the body after the external stimulus is withdrawn, the injurious exposure continues. In these cases, "injury," albeit infinitesimal, could be said to be ongoing throughout the period of time when the toxic agent remained in the body. As long as the injurious exposure continued, a court could plausibly apply a continuous trigger despite the existence of the risks,

unknowns, and improbabilities of cancer development discussed in this article. This is, in essence, what courts appear already to have done with respect to coverage for asbestos-related cancers.

B. *When the Offending Agent Does Not Remain*

Where the offending agent does not remain in the body, as in cases of exposure to human carcinogens like radon,²¹⁶ vinyl chloride,²¹⁷ and ethylene oxide,²¹⁸ the situation is more problematic. In such cases, courts can only be reasonably sure that an injury "in fact" has occurred during the periods of exposure to the toxic agent and during the period when a tumor has appeared or where it becomes more probable than not that a tumor will appear. But here, two problems arise. First, science at this point cannot determine when it becomes more probable than not that a group of cells with mutations will become cancerous. Second, a tumor may exist for some time before it is detected or detectable.²¹⁹

Scientific advances in cancer detection, however, may ameliorate some of this problem. The recent advances in the use of CT scans to image lung cancer tumors has permitted physicians to detect tumors the size of a grain of rice instead of the size of an orange, as detectable with traditional chest X-rays. While the use of the CT scan technique is still preliminary, it may detect lung tumors two to three years earlier than before, and at a time when they may be successfully removed. This boosts the survival rate by up to eighty percent.²²⁰ Although the CT scan technique is far more important to patients and clinicians than it is to coverage

216. See INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 43 IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS 173-259 (1988) (This section evaluates radon).

217. See GREEN & HATHWAY, *supra* note 215.

218. See INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 60 IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS 73-159 (1994) (This section evaluates ethylene oxide).

219. The court in *Eagle-Picher Industries v. Liberty Mutual Insurance Co.*, 829 F.2d 227 (1st Cir. 1987), described similar problems in determining when asbestos-related diseases were diagnosed and/or diagnosable.

220. See Claudia I. Henschke et al., *Early Lung Cancer Action Project: Overall Design and Findings from Baseline Screening*, THE LANCET, July 10, 1999, at 19-105; EMMA ROSS, *Study Suggests More Precise Lung Cancer Screening Could Save Lives* (July 9, 1999) <<http://www.sfgate.com/cgi-bin/article.cgi?file=/news/archive/1999/07/09/international1043EDT0577.DTL>>.

analysts, this and other advances in screening and detection methods may make coverage analysis less hazardous. Other early cancer detection methods that may help ascertain when cancer becomes probable involve testing saliva, stools, or urine for the presence of aberrant proteins present in cells shed by the cluster of mutated cells.²²¹ Similar techniques hope to detect cancer through the presence of the enzyme telomerase, which permits cells that normally would die to become immortal and cancerous.²²² Though it is difficult to predict at this time which test or screening measure will work for which cancer, there is reason to believe that at least some of the major problems associated with assigning a date of injury to cancer might soon be significantly ameliorated.²²³

C. *Fair and Straightforward Application of the Continuous Trigger*

In the meantime, courts that profess to apply the continuous trigger on the basis of continuous injury should employ the standard fairly and straightforwardly. This means that if there is no competent factual basis for finding injury during the latency period after injurious exposure to a substance has ceased, but before symptoms appear, then coverage should not be triggered during that time.

The Illinois Supreme Court in *Zurich Insurance Co. v. Raymark Industries, Inc.*²²⁴ reached such a conclusion. It affirmed a trial court ruling that denied application of a continuous trigger to the latency period between exposure to asbestos and the appearance of the physical symptoms of asbestos-related diseases or injuries. The Illinois Supreme Court upheld the trial court's ruling because the evidence was simply insufficient to support the blanket conclusion sought by the insured that asbestos-related "disease progresses in every case after exposure ceases."²²⁵

By contrast, in the first opinion to apply the continuous trigger, the *Keene* court dispensed with any detailed review of the factual developments of asbestos-related diseases. It did not need such evidence because as the court candidly

221. See WEINBERG, *supra* note 5, at 157-58.

222. See SCI. AM., *supra* note 58, at 62.

223. See *id.* at 65; WALDHOLZ, *supra* note 71.

224. 514 N.E.2d 150 (Ill. 1987).

225. *Id.* at 160-61.

explained, it would apply a continuous trigger from the moment of first exposure until the appearance of disease symptoms even if "no cellular changes were known to occur during [the latency] period."²²⁶ Courts that have based the application of a continuous trigger on the determination that injury continues through each policy period do not have the *Keene* option. They should not resort to legal fiction and use the so-called retrospective analysis, in effect, to adopt the *Keene* approach, while claiming to be guided by the "facts."

226. *Keene Corp. v. Insurance Co. of N. Am.*, 667 F.2d 1034, 1044 n.19 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1007 (1982).