The Use and Abuse of the Doubling Time Theory in Cancer Litigation

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In lawsuits involving plaintiffs afflicted with cancer, litigators desire a scientific principle which can be used to determine when the disease first developed. If a model existed which could measure the growth process of cancer cells, then:

- a medical malpractice plaintiff would be able to establish that the tumor was of a certain detectable size at an earlier date of examination when the alleged malpractice occurred;
- a medical malpractice defendant could demonstrate that the cancer existed for a long time and had metastasized prior to the date of malpractice, and that failure to detect was not the proximate cause of any measurable injury to the plaintiff; and
- a toxic tort defendant could prove that cancer existed before exposure.

Attorneys thought they discovered this model in the "doubling time" theory. See Collins, V., "Observations on Growth Rates of Human Tumors," *Amer. J. Roent.* 76:488 (1956). The theory, attempting to provide a model for the growth of cancer cells, has been applied in cases involving lung cancer [see, e.g., *Boody v. United States,* 706 F.Supp. 1458 (D. Kan. 1989); *Johnston v. United States,* 597 F.Supp. 374 (D. Kan. 1984)]; adenocarcinoma of the cervix [see, e.g., *Beckcom v. United States,* 594 F.Supp. 1471 (N.D.N.Y. 1984); *Snead v. United States,* 595 F.Supp. 658 (D.C. 1984)]; and breast cancer, where it has its widest application—or, more appropriately, misapplication [see, e.g., *Sacco v. Roupenian,* 564 N.E.2d 386 (Mass. 1990); *Shapiro v. Burkons,* 404 N.E.2d 778 (Ohio App. 1978); *Thor v. Boska,* 113 Cal. Rptr. 296 (Cal. App. 1974)].

The doubling time theory has been most often advanced in the proximate cause context where there is a delay in the diagnosis or institution of appropriate treatment and where it is difficult to deny the existence of malpractice. In this situation, experts generally attempt to work the formula backwards. See, e.g., *Sacco v. Roupenian,* 564 N.E.2d at 388; *Thor v. Boska,* 113 Cal. Rptr. at 299. Based on *one* particular measurement at a given time, they reach a conclusion as to prognosis when the alleged malpractice occurred, and thus "demonstrate" a lack of proximate cause between the injury and the failure to make a timely diagnosis. *Id.; Boody v. United States,* 706 F.Supp. at 1461; *Beckcom v. United States,* 584 F.Supp. at 1480-82. The theory also has been employed to prove that a particular agent did not cause injury because the cancer existed prior to the exposure to the agent. See, e.g., *Johnston v. United States,* 597 F.Supp. at 420-428.

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Outside of the proximate cause context, plaintiffs and defendants most frequently apply the theory to demonstrate whether or not a lesion was present at the time the defendant physician conducted his examination. See, e.g., *Nussbaum v. Gibstein,* 531 N.Y.S.2d 276 (App. Div. 2d Dept. 1988); *Snead v. United States,* 594 F.Supp. at 665-66.

Although the doubling time theory has been, and continues to be, a model which litigants are quick to invoke, its lure and seeming simplicity lead many practitioners to misapply it. The biggest abuse is when it is introduced in breast cancer cases where, because of the absence of adequate tumor measurement at the time of the alleged malpractice, the growth rate is unknown and a "median time" is applied. Ignoring that breast cancer doubling time ranges anywhere from 28 to 900 days depending on methodology, litigants attempt, and unfortunately more often than not get away with, introducing speculative evidence far beyond the range of scientifically accepted standards. It has also been used by medical malpractice defendants as a means to introduce the concept of metastases to a jury, which usually equates this with death. In addition, litigants rely on the theory as it was originally formulated in 1956 without recognition of subsequent mathematical modifications which comport the theory with clinical data. See, e.g., *Boody v. United States,* 706 F.Supp. at 1461. The unwary are forced to respond to the application or misapplication of the "doubling time" theory with experts who testify that the theory:

> "... was just that, a theory postulated by 'certain doomsday prophets.' Its ultimate conclusion was that there was no need to treat cancers 'because some people will live with their cancers for 40 years and some people will die of their cancers in four months.' The theory cannot be relied on 'in any

single human case' because many different factors affect the growth rate of cancer."

Thor v. Boska, 113 Cal. Rptr. at 299 (citing plaintiff's expert's testimony). This response, though broadly accurate, is often too simplistic. Doubling time does have a use, but its use is limited to those situations where the scientific data show that doubling time of a *particular* cancer is within a narrow range so that the application of a mean value has medical probability of accuracy. See *Johnston v. United States*, 597 F.Supp. 374. Doubling time is *inapplicable* where litigants seek to invoke the theory the most: in breast cancer cases where there is only one tumor measurement—at the time of removal. This article is designed to assist practitioners by instructing when and how to apply contemporary cancer growth curve kinetics in applicable cancer cases.

RELATIONSHIP BETWEEN TUMOR SIZE AND AXILLARY NODE INVOLVEMENT AND 5-YEAR DEATH RATES IN BREAST CANCER PATIENTS

	Tumor Size (cm)				
	≤1.0	★1.0 - 1.9	2.0 - 2.9	3.0 - 4.9	≥5.0
Positive Nodes	20%	38%	41%	50%	60%
5-Year Deaths	18%	23%	27%	43%	57%

Source: Henderson, I.C. et al., "Breast Cancer," *Cancer: Principles and Practice of Oncology*, V.T. DeVita et al. (eds.) 1197-1268 3rd ed. (1989).

Table 1

The original doubling time theory. Cancer cells grow by binary fission, i.e., division into two equal cells. The time it takes one cell to become two cells is the doubling time and is considered one doubling. According to the theory as originally formulated, cancer cell growth is considered constant for both primary and metastatic tumors. The formula to determine the number of cells present at any time interval is 2^N, where "N" equals the number of doublings. Thus, at the twentieth doubling, i.e., 2^{20}, there are one million tumor cells. This growth process is considered mathematically as exponential.

Applying the classic breast cancer model, an individual cancer cell is generally assumed to be an average 1,000 cubic microns in size. When this "average" cell size is applied to a tumor at any particular doubling, a three-dimensional sphere shape is *hypothesized. Johnston v. United States*, 597 F.Supp. at 385. Therefore, 2^{30} cells (at its thirtieth doubling) would have a diameter of one centimeter, contain one billion cells, and be considered the minimum size palpable by a physician.

Mathematically, exponential cell growth can be expressed by the following formula assuming unperturbed tumor growth:

$$N(t) = N(o) \exp (bt)$$

See Skipper, H. and Schabes, Jr., F., "Quantitative and Cytokinetic Studies in Experimental Tumor Systems," *Cancer Medicine*, J.F. Holland and E. Frei (eds.) 636-648 2d ed. (1982). In this equation, the cell number ("N") is a function of the starting size of the tumor ["N(o)"]; the time of growth ("t") and a constant ("b"). The exponential pattern of cell growth can be useful *in vitro*, but must be modified to comport with actual clinical data.

The Gompertz equation for doubling time. In an attempt to account for the doubling time variability, the original doubling time formula was modified into the "Gompertz equation." This different mathematical version of the doubling time theory can be applied to a tumor growth curve with significantly better accuracy in evaluating growth given *two* points in time. As with the original doubling time hypothesis, in Gompertzian growth, doubling time, "N(t)" is a function of "N(o)," "t," and "b," but adds a limiting tumor size "N(∞)" by the equation:

$$N(t = N(o) \exp \{K [1-\exp(-bt)]\}$$

where $K = \log_e [N(\infty)/N(o)]$. This equation fits experimental research models,[1] clinical data,[2] and growth regulatory mechanisms.[3]

This new version of the doubling time theory comports with clinical data which indicate that a tumor has different growth rates during its life span. See *Boody v. United States*, 706 F.Supp. at 1458 ("The tumor grows very fast up to about one centimeter in size and then its growth rate begins to slow down . . . and metastases grow faster than primary tumors."). Some experts distinguish these different growth rates as "slow doubling" (approximately every 309 days for breast cancer), and "fast doubling" (approximately every 23 days for breast cancer). *Jones v. Smith*, 1986 WL 15311 at 3. Epidemiological data relating the carcinogenic influence of primary carcinomas to the incidence of breast cancer suggest that the duration of precancerous growth is significantly longer than doubling times. See Tokunaga, M. et al., "Malignant Breast Tumors Among Atomic Bomb Survivors," *J. Nat. Can. Inst.* 62:1347 (1979). The Gompertz equation *is not* applicable to the precancerous state induced by carcinogens since a second random event is involved before Gompertzian growth of any tumor.

Thus a line representing a breast cancer tumor's growth on a graph would appear to have a steep quick rise and then level off into a very slow, gradual, almost horizontal line. This decrease in the doubling time (termed an "asymptotic plateau"), is not due to a decrease in blood supply or other artifacts of size, but is due to a tumor's intrinsic nature to behave like a normal human organ. The Gompertz equation thus corrects the original doubling time theory's assumptions of uniformity in cell growth and that a tumor consists of a pure population of cancer cells unperturbed by its interval milieu.

Original doubling time versus the Gompertz equation. In *Boody v. United States*, 706 F.Supp. 1458 (D. Kan. 1989), the Gompertz equation was employed to challenge the original doubling time theory in court. *Boody* involved a medical malpractice action against Air Force doctors for failing to diagnose lung cancer based on an X-ray. The estate claimed that, as a result of the delay, the tumor metastasized to the brain and resulted in the patient's demise. In the defense's corner was Dr. Vincent Collins, a pioneer in the development of the original doubling time theory.[4] Applying the original and unmodified theory, he calculated that the decedent's lung tumor had been present for eight years before the defendant's X-ray was taken, during which time metastasis had occurred. Dr. Collins thus opined that the defendant's failure to properly diagnose the cancer would not have affected the timing of her ultimate tragic outcome.

The plaintiffs counterpunched with

5-YEAR RELAPSE RATE (%) ACCORDING TO TUMOR SIZE/NODES

	Tumor Size (cm)		
	≤2.0	2.0 - 5.0	★5.0
Zero Nodes Positive	8 - 12%	19 - 24%	19 - 27%
Positive Nodes	37 -50%	50 - 60%	65 - 79%

Source: Henderson, I.C. et al., "Breast Cancer," *Cancer: Principles and Practice of Oncology,* V.T. DeVita et al. (eds.) 1197-1268 3rd ed. (1989).

Table 2

the Gompertz equation.[5] Their expert criticized the original doubling time theory which did not have the mathematical modifications necessary to comport the theory to clinical data. Explaining that tumors have different growth rates and metastases grow faster than primary tumors, the plaintiff's expert expressly disagreed that metastasis occurred eight years before the initial X-ray. The plaintiff's expert could not exactly state when metastasis occurred; however, he opined that the defendant's failure to detect the lung tumor significantly diminished the chances of tumor removal before metastasis. The "decedent had a five-year survival rate of 51 percent because of the unlikelihood her lung tumor had metastasized." 706 F.Supp. at 1461-62.

After evaluating both of the battling experts, the court found that the Gompertz equation more closely reflected actual cancer growth based on its relation to clinical data. Finding that the doubling time theory was a useful device in determining cell growth, the court favored the Gompertz equation as a more accurate and realistic measure of cancer growth over the original unmodified theory. This case should have marked the death knell for the original doubling time theory. Experience, however, teaches that the original doubling time theory is still employed. Unfortunately, fundamental criteria for employing the doubling time theory are often ignored.

Misapplication of doubling time. Something happened to the "doubling time" theory when brought into the courthouse. Dr. Collins made it clear that in order to determine accurately the doubling time rate in any *individual* case, one needed to know the size of the tumor at *two* distinct periods of time. *Boody v. United States,* 706 F.Supp. at 1461. This principle is necessary for the Gompertz equation as well. See, e.g., *Sacco v. Roupenian,* 564 N.E.2d at 388. Because a defendant's malpractice often meant that the lesion was not adequately appreciated when the patient presented to the doctor, measurement of tumor size often first occurs at the time of surgical diagnosis. Therefore, defense experts resorted to using a "median doubling time," usually of 100 days [see, e.g., *Jones v. Smith,* No. 2237 (Ohio App. Dec. 31, 1986) (1986 WL 15311) at 3], to "demonstrate" that the tumor has been growing in the patient for approximately eight years, i.e., 100 days × 30 doublings = 3,000 days (see, e.g., *Boody v. United States,* 706 F.Supp. at 1461). They then argue that if by the fortieth doubling breast cancers are fatal, the amount of time between first clinical detection of the tumor by palpitation and the most likely time of death is only three years (10 doublings at 100 days) compared with a preclinical history of eight years.

The use of a median doubling time is inappropriate to any individual breast cancer case because the range is too broad and, hence, its use injects excessive speculation into the expert's opinion. The generally accepted medical opinion is that doubling time is *not* constant. See Laird, A.K., "Dynamics of Growth in Tumors and in Normal Organisms," *Nat. Can. Inst. Mono.* 30:15 (1969). Variability in cancer growth rates are thus effectively ignored when a "median time" is applied in cancer cases with wide fluctuation in Gompertzian doubling time. Numerous generally accepted scientific studies state that doubling times in breast cancers range between 28-900 days depending on methodology. See Lundgren, B., "Observations of Growth Rate on Breast Carcinomas," *Cancer* 40:1722 (1977) and Ingleby, S. and Gershon-Cohen, L., *Comparative Anatomy, Pathology and Roentgenology of the Breast* 388 (1960). See also *Nussbaum v. Gibstein,* 531 N.Y.S.2d at 279 ("studies measuring the growth rate in the human breast as opposed to the laboratory have shown doubling times ranging from 20 to 209 days); *Borgren v. United States,* 716 F.Supp. at 1381 (80 to 210 days). The use of median time in the doubling theory equation for breast cancer cases should cause the expert's opinion to be inadmissible since it is too speculative.

Countering abuse of doubling time. When a median time is chosen by an adversary's expert, it is therefore important for the litigator to know how to discredit its use. For example, when an expert attempts to use a 100-day median time in breast cancer cases, the plaintiff should argue that the median time is purely speculative when used to satisfy a variable in the application of a theoretical equation to a given individual. This contravenes the law's prohibition against speculative expert opinion. Median times are *only* appropriate where the range associated with a tumor type is sufficiently small to state scientific probability. See *Johnston v. United States,* 597 F.Supp. at 428-29; *Chudson v. Ratra,* 548 A.2d 172, 179 (Md. App. 1988). This speculation using median times should be enough to defeat an attempted application of the doubling time theory. *Chudson v. Ratra,* 548 A.2d at 179; *Richardson v. Richardson-Merrell, Inc.,* 649 F.Supp. 799, 803 (D.D.C. 1986) ("without a genuine basis 'in or out of the record' . . . expert 'theoretical speculations' are insufficient to sustain" the proponent's burden of proof). Clearly, only the Gompertz model of tumor growth has been subjected to clinical

In *Borgren v. United States,* 716 F.Supp. at 1381, the court acknowledged the general correlation between tumor diameter and the number of doublings:

Number of Doublings	Tumor Diameter
0	one cell
13	0.5 mm
20	1.0 mm
30	1.0 cm
35	3.0 cm

The value of mammography is that it provides a vehicle for detecting lesions at 0.5 centimeters before they are palpable. See, e.g., *Jones v. Smith,* 1986 WL 15311 at 3.

Table 3

scrutiny and should be the scientific model applied in the courts. See Norton, L., "A Gompertzian Model of Human Breast Cancer Growth," *Can. Reg.* 48:7067 (1988).

Only when the size of a breast tumor is known at *two* separate time intervals, and hence there is no need to resort to median growth rates, can the doubling time theory be practically used and applied in a scientifically meaningful fashion. In addition, litigants should consult with their experts to evaluate the growth periods of various tumor sizes to determine whether they vary significantly at different levels of their lives.

In malpractice cases in which metastatic disease results after the alleged negligent act, the defense may attempt to misuse the doubling time to demonstrate that metastasis growth was the same as the primary breast cancer. It should be countered with the scientific studies demonstrating that lung metastases of primary breast cancers have a double time range of 10-165 days[6] and skin metastases have a double time range of 3-86 days. Thus, in general, the doubling time for metastatic breast cancer cells is much faster than the primary tumor. Similarly, tumor metastatic to lymph nodes have a 2-20 times greater growth rate than the primary tumor, significant in cases involving regional node (axillary) internal mammary metastasis. See *Boody v. United States,* 706 F.Supp. at 1461. As with primary tumor growth, the defendant cannot usually use a median time for metastasis.

If the defense is permitted to use a median doubling time of 100 days for the primary tumor, then it must use 5-50 days for the doubling time of cancer in lymph nodes so that the use of a median doubling time can be used to attack the opinion given. A regional lymph node positive at the time of diagnosis may have been negative at the time of the alleged negligence. See American Joint Committee on Cancer "TNM Staging" (1988). This is critical to establish damages since ten year disease-free survival for women treated with surgery *alone* was 75 percent with no positive nodes, 38 percent for 1-3 positive nodes, and 12 percent with greater than 3 nodes positive. See Fisher, B. et al., "Ten-Year Follow-Up Results of Patients With Carcinomas of the Breast," *Surg. Gyn. Obstet.*140:528 (1975).

Additionally, even though a metastasis to regional nodes may already be present at the time of or prior to the alleged negligent act, a delay in treatment may significantly increase the likelihood of cancer dissemination to other areas of the body that make prolonged survival unlikely. For example, patients without axillary lymph node metastasis "(N_0)" have a better prognosis than those with axillary lymph nodes "($N_{1,2}$)" which have a better prognosis than patients with distant metastasis "(M_1)." By delaying treatment of the primary breast tumor and regional lymph nodes, a continuous source of cancer cells will be present to seed vital areas, like the lung, liver or brain. The metastasis significantly shortens life expectancy. Hence, in those jurisdictions which permit recovery for a lost chance, practitioners should be alert to the conclusions which can be drawn from an application of the doubling time theory.[7]

Caveats. There are additional points which must be emphasized to avoid future misapplication of the "doubling time" theory. First, "doubling time" is not recognized by a consensus of the medical community as a method for determining prognosis or modality of treatment. See *Waffen v. U.S. Department of Health & Human Services,* 799 F.2d 911, 921 (4th Cir. 1986). All that doubling time describes is the growth process of cancer cells. The generally accepted scientific model for determining prognosis and modality of treatment is the tumor/nodal involvement/metastases ("TNM") staging protocol which describes the anatomic progression of the cancer at the time of diagnosis. See, e.g., *id.* at 920. TNM staging compares three factors: (1) the size of the primary tumor ("T"); (2) the status of the regional lymph nodes ("N"); and (3) the presence or absence of distant metastases ("M"), which are secondary tumors arising from the spread of cancer cells through the bloodstream and the lymphatic channels from the primary tumor. See American Joint Committee on Cancer "TNM" Staging (1988).

Second, by the time a breast cancer lesion reaches one centimeter (at its 30th doubling) and is palpable, clinically detectable metastasis probably has not occurred. See Tables 1 and 3. The defense will nevertheless work the doubling time theory backwards in an attempt to persuade the factfinder that metastasis, albeit *subclinical,* had already occurred at the time of misdiagnosis when the lesion was already one centimeter. This frequently occurs when the lump size at the time of the failure to diagnose examination is not recorded, but there is a measurement at the time of surgical removal. See, e.g., *Boody v. United States,* 706 F.Supp. at 1461; see also Table 3. The plaintiff should be able to counter successfully that subclinical metastasis is not related to staging, i.e., survival, since the TNM staging deals only with *clinical* observations. Staging and prognosis based on a retrospective application of the doubling time theory is pure speculation even accepting the existence of subclinical metastases. Similarly, statistics comparing tumor size ("T") and the probability of axillary node metastasis clearly favor the patient with the smaller lump. See Tables 1 and 2.

Conclusion. Doubling time should be applied using the contemporary Gompertz equation which more accurately reflects clinical data. Notwithstanding using the right formula, the doubling time theory's application is limited to those cases where the range of possible growth rates are so narrow that the use of a median time would not have a significant statistical deviation. The theory is *always* inappropriate in breast cancer cases where only one accurate measurement is known.

Endnotes

1 See Simpson-Herren, L and Lloyd, HA, "Kinetic Parameters and Growth Curves for Experimental Tumors," *Can Chemo Rep* 54:143 (1976).

2 See Sullivan, PW and Salmon, SE, "Kinetics of Tumor Growth and Regression in IgG Multiple Myeloma," *J Clin Invest* 51:1697 (1972).

3 See Demicheli, R, "Growth of Testicular Neoplasm Lung Metastasis," *Eur J Can* 16:1603 (1980).

4 Indeed, Dr. Collins is recognized as having written the "seminal article" on the topic and is regarded as the "first person to use the term 'doubling time' to describe the growth of cancer." *Johnston v. United States,* 597 F.Supp. at 420.

5 Although not acknowledged in the case as the "Gompertzian equation," a review of the techniques employed by the plaintiff's expert clearly shows that this was the formulation applied.

6 This is distinguished from the most common lung cancer, i.e., squamous cell carcinoma, the doubling time of which ranges from 30 days or less to 90 days or more. *Johnston v. United States,* 597 F.Supp. 427.

7 As to damages for lost chance, *see Evers v. Dollinger,* 471 A.2d 405 (N.J. 1984) and the cases cited therein.

Bits on M.D.s...

Medicine is a collection of uncertain prescriptions, the results of which, taken collectively, are more fatal than useful to mankind. Water, air and cleanliness are the chief articles in my pharmacopoeia.

Napoleon Bonaparte