Collins V P, Loeffler R K & Tivey H. Observations on growth rates of human tumors.
Amer. J. Roentgenol. **76:**988-1000, 1956.
[Baylor University College of Medicine, Department of Radiology, Houston, TX]

Linear exponential growth, determined by measurement of pulmonary metastases and expressed as 'Doubling Time,' is introduced as a characteristic of the individual cancer, governing the duration before and after diagnosis. The evidence for an age-related 'Period of Risk' for childhood tumors is a supporting application. [The *SCI®* indicates that this paper has been cited over 165 times since 1961.]

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"The origin of the concept of linear exponential growth as a governing characteristic of cancer cannot be recalled but the thesis was developing, and data accumulating, from 1950 on under the influence of the varied background of the authors in pathology [Collins], physics [Tivey], mathematics and bio-statistics [Loeffler]. Simply stated, the rule to be tested was that the growth of cancer was linear and exponential with a constant growth rate, as a characteristic of the individual cancer as its morphology, governing the duration of cancer before and after the time of diagnosis. With confirmation of clinical applicability, the literature has given the accolade of 'law,' better perhaps than Murphy's but not as reliable as Newton's. The ultimate acceptance must be ascribed to its simplicity and clinical applicability. Growth is a synonym for cancer. Growth is a function of time and increasing volume and both are measurable. There is a ready measure of growth rate in 'doubling time.'

"The rule explains the phenomenon of the dormant cancer; the total duration of cancer is approximately 40 doublings; three quarters of this time is in the period of silent, steady growth that occurs before the recognition of the small (but not early) cancer. It explains the phenomenon of the cancer 'that suddenly began to grow wildly;' this is the exponential upsweep after 35 to 40 doublings. It explains the paradox of earlier diagnosis and ever-improving survival rates but unrelenting mortality rates, such as characterize breast cancer. To move diagnosis to the left on the exponential curve is to start the countdown on survival at an earlier point in time, to increase survival time even without treatment, and to mask the effect of treatment with unearned credit.

"There is particular appeal in the implications for childhood tumors. The 'Period of Risk' thesis (that recurrence, if going to occur, should develop within a period equal to the age at diagnosis plus nine months) evolved in a search for justification for extrapolation of linear exponential growth back to the time of inception; several series seem to corroborate the rule. It also un-masks the error in assuming that childhood tumors are uniformly malignant and rapidly growing for lack of a sturdy host reaction. In this age group all tumors must grow rapidly; a child is not old enough for a slowly growing cancer to have reached the size of recognition; slowly growing cancers have not had time to traverse their characteristic period of silent growth when this is greater than the age of the child.

"Simplicity was the merit of the thought and the obstacle to its acceptance. On first submission for publication, it was returned with a comment to the effect that 'I have read this through twice and would not touch it because we do not accept this sort of material.'

"In the arena of cancer research the initial impact was approximately that of a presentation on fire-making with two sticks, offered at a convention of nuclear physicists. The simplicity of the hypothesis does assault the accepted infinite complexity of etiology, biochemistry and cyto-kinetics of cancer. But until nuclear physicists solve our energy problem, there is some practical application for the warmth of a small fire kindled with two sticks."