This Week's Citation Classic®

Nowell P C. The clonal evolution of tumor cell populations. *Science* 194:23-8, 1976.
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This article proposed that most neoplasms are unicellular in origin and that tumor progression often results from acquired genetic instability in the original clone. This allows sequential selection of more aggressive sublines and leads to considerable heterogeneity and individuality in advanced malignancies. [The *SCI*® indicates that this paper has been cited in over 715 publications.]

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October 6, 1987

A continuing attempt to understand the neoplastic process has been the basis of my 35-year career in cancer research. This article was an extension of concepts developed in the 1950s by workers who examined (from a biological[1] standpoint and from a cytogenetic[2] standpoint) the phenomenon of tumor progression—the tendency of neoplasms to become more aggressive in their behavior and more "malignant" in their characteristics during their life history.

By the 1960s my own work in tumor cytogenetics and in radiation carcinogenesis[3] helped crystallize my thinking, and I found over the next decade that the resultant model of tumor development was very useful in my introductory lectures on neoplasia to medical students. As finally written for *Science* in 1976, the views were hardly revolutionary, although some diehards were still resisting the idea that tumors resulted from somatic genetic change.

I cited cytogenetic and other evidence to support the concept that tumors arise from a single "mutated" cell and that biological and clinical progression results from subsequent additional alterations, giving rise to more aggressive subpopulations within the original neoplastic clone. More controversial was the additional suggestion that the likelihood of such sequential genetic changes in tumor cells was enhanced by increased genetic instability in these cells, acquired as part of the neoplastic process. I suggested several possible mechanisms for this increased lability but was able to provide little firm evidence.

The initial reaction to this article was generally favorable despite its rather pessimistic implications for simple answers to cancer therapy. Subsequent work, particularly on the molecular genetics of neoplasia, has confirmed much of the clonal evolution concept, and it is increasingly clear that sequential involvement of critical genes underlies many aspects of tumor development.[4] Most of these recent studies have dealt with genes involved in growth regulation (oncogenes), and in a recent update of the 1976 paper[5] I suggested that the time is now ripe for molecular genetic investigation of other key aspects of tumor progression, such as how the malignant cell acquires the capacity for invasion and metastasis. Interestingly, relatively little new information has been learned on the nature and extent of acquired genetic instability in tumor cells, although considerable progress has been made on the molecular basis of constitutional chromosomal fragility.[6]

The "clonal evolution" article appears to have been widely cited because it provided a reasonable framework within which to investigate and discuss various aspects of neoplasia. As such, it may have been useful, but success in dealing with the cancer problem must ultimately lie in precise characterization of the somatic genetic events and related host responses, which this model only suggested.

1. **Makino S.** Further evidence favoring the concept of the stem cell in ascites tumors of rats. *Ann. NY Acad. Sci.* 63:818-30, 1956. (Cited 50 times.)
2. **Foulds L.** Tumor progression. *Cancer Res.* 17:355-6, 1957. (Cited 10 times.)
3. **Cole L J & Nowell P C.** Radiation carcinogenesis: the sequence of events. *Science* 150:1782-6, 1965. (Cited 80 times.)
4. **Klein G & Klein E.** Evolution of tumors and the impact of molecular oncology. *Nature* 315:190-5, 1985. (Cited 210 times.)
5. **Nowell P C.** Mechanisms of tumor progression. *Cancer Res.* 46:2203-7, 1986.
6. **Nicolson G L.** Tumor cell instability, diversification, and progression to the metastatic phenotype: from oncogene to oncofetal expression. *Cancer Res.* 47:1473-87, 1987.

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