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Tumor dormancy: separating observations from experimental science

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The articulate review by Demichelli *et al*. in this issue of the journal goes beyond identifying deficiencies in our current understanding of breast cancer, to state a provocative hypothesis.[1] The authors contend that continuous growth of cancerous masses cannot explain the observed time durations between primary resections and local or distant recurrences or deaths. They then posit that the growth curves must be interrupted by variable periods of dormancy. Furthermore, they argue that surgical removal of a primary tumor might shorten durations of dormancy and thereby promote the appearance of metastases. Such intended iconoclasm demands attention, even if the contained details evoke vigorous disputation.

The term 'dormancy' is linked to the idea of delayed angiogenesis, which is a tenable, perhaps conventional argument. But dormancy, whether tenable or not, must be recognized as an expedient mathematical device. If Johnny leaves home to go to the grocery store—a journey that usually takes 10 minutes—and arrives at the store 20 minutes later, it is convenient to hypothesize that he took a 10 minute rest somewhere, ambulatory dormancy as it were. Did anyone see him resting? Perhaps he took a longer route intentionally or inadvertently, or consumed time in a manner that was far from dormant. Hence, in reacting to Demichelli's thesis, we need to separate the observations—mysterious time delays—from the proposed explanation: unstable dormancy.

Indeed, we may accept that simple growth models are probably inadequate to explain the complexity of cancer in all of its myriad manifestations, even if we have seen such models generate hypotheses that were tested successfully in the clinic.[2] We also know that slow growth has been observed in experimental models, although this is usually more the consequence of high cell-death rates than low mitotic rates.[3] In addition, the mitogenic impact on residual cancer foci of surgery is a venerable observation, explainable only by circulating factors.[4] That these authors have grouped these disparate items into a cohesive, if incomplete, package is commendable, especially as they clearly label their ideas as hypothetical and identify many unanswered questions in their closing discussion. Hence, they thereby appropriately allow the reader to neither accept nor dismiss their thesis outright, but to use it as a springboard for creative thought and, ideally, experimental exploration.

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Of course, until theoretical models make valid predictions under a variety of laboratory and clinical conditions, they cannot be regarded as close enough approximations of reality to influence therapeutic decisions. I know of one case in which a patient refused primary surgery for her proven breast cancer for fear of stimulating metastases, a decision with predictably disastrous consequences. Our job is to examine Demichelli's dormancy thesis through the lens of experimental science, duly considering alternative ideas. In that regard, a view of cancer as a disease of self-seeding has recently been proposed, which explains continuous Gompertzian growth once growth commences, but also allows for seeming growth delays by virtue of cancer cells' random wanderings, intermediate stops including transient returns to the organ of origin, and inhibited extravasations at the 'locked doors' of latent metastatic sites.[5] Surely, angiogenesis via circulating endothelial cells may have a role[6]—as stipulated in Demichelli's hypothesis. These are testable ideas. There is a time at which observation-motivated theoretical musing must stop and investigation-dependent mechanistic elucidation must begin, and the Review by Demichelli *et al*. may well signify that time has come.

L Norton is an Advisory Board member of Nature Clinical Practice Oncology.

Competing interests
The author declared no competing interests.

www.nature.com/clinicalpractice
doi:10.1038/ncponc1001

Supplementary information in the form of a reference list is available on the *Nature Clinical Practice Oncology* website.