Focusing on Preinvasive Neoplasia

To the Editor.—To “reduce cancer mortality on a population scale,” we must acknowledge our failures in the war on cancer, initiated in the United States by President Nixon in 1971. Despite tremendous expenditures of money and brainpower, we are still unable to effectively treat many otherwise healthy people with advanced disease. This may be because our reductionist model of biology is inadequate. Reductionism states that the behavior of the whole is equal to the sum of the behavior of the parts; that sophisticated systems are merely combinations of simpler systems and that pathophysiology is linear and predictable. In contrast, Kauffman, Bak, and others propose that life arose and continues based on nonlinear flows discussed as complexity theory or self-organized criticality. In complex systems, including humans, novel properties emerge that cannot be predicted from studying each part separately and are best understood by analyzing patterns of behavior.

Tumors with no known morphologic precursor lesion most likely do have precursors that are identifiable based on patterns of molecular activity. Complexity theory indicates that living systems arise based on hierarchies, in which a combination of agents (genes, proteins, or processes) at one level become agents themselves at the next level. For example, DNA transcription and translation produce proteins, which then interact to form organelles, which cluster to create cells, which interact to form tissues. I have proposed that cancer typically arises due to 9 chronic stressors that find “weak spots” in cellular networks that cause them to deviate from their usual physiologic state. These local network changes may interact to create a hierarchy with new biologic properties called an attractor, which acts as an intermediate state. Molecular investigation may identify these premalignant patterns in gliomas and other tumors with no identifiable histologic precursor lesion.

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