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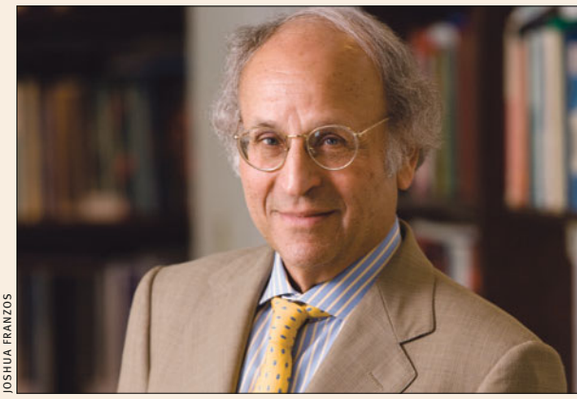
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JOSHUA FRANZOS

I don't particularly care about the usual. If you want to get an idea of a friend's temperament, ethics, and personal elegance, you need to look at him under the tests of severe circumstances, not under the regular rosy glow of daily life. Can you assess the danger a criminal poses by examining only what he does on an ordinary day? Can we understand health without considering wild diseases and epidemics? Indeed the normal is often irrelevant. —Nassim Taleb

You may be familiar with the ideas of Taleb, author of *The Black Swan* (not the ballerina film with Natalie Portman; Taleb's subtitle is *The Impact of the Highly Improbable*). In his book, he discusses how rare "shocks and jumps" have great consequence in social, political, and financial life. Incidents like the rise of the Internet or of Hitler or of a particular school of art don't fit into the normal Gaussian "bell curve" embraced by scholars of social science and economics. Yet, Taleb notes, their potential impact is almost always profound, and failing to account for the possibility of such "Black Swans," as he calls them, can lull us into believing we've tamed uncertainty.

Game-changing outliers also make themselves known in the natural world. Consider the virus that unexpectedly jumps from chicken to human, threatening a worldwide epidemic. Or how variation among species, like an addition of a lens in a trilobite's eye, is likely to happen suddenly, rather than gradually, often because of new environmental pressures. By "suddenly," I'm referring to the geologic time scale, perhaps over 50,000 or 100,000 years. Stephen Jay Gould and Niles Eldredge articulated this theory of "punctuated equilibrium" in 1972. Their proposal challenged an interpretation of Darwin's theory of evolution as a gradual progression.

As technology has progressed and allowed us to interrogate in great detail the genomes of tumors, we are seeing the same evolutionary patterns on the molecular time scale—at hyperspeeds. A recent report from a team of researchers at Cornell, Harvard, and Trento universities shows mutations in prostate tumors occurring in abrupt, periodic bursts, causing complex, often wholesale reshuffling of DNA—punctuated equilibrium in cancer! With this revolution in their genomic structure (356,000 base-pair mutations and 5,600 rearrangements among 57 tumor genomes!), the tumor cells were more likely to adapt and survive. Here again we see how "shocks and jumps" in the natural world have profound implications. It's as though cancer cells do whatever it takes to survive, and may do so very quickly. Viruses also may show "shocks and jumps." For example, HIV, in one infected person, may develop many mutations in weeks. This is why single drugs with single mutations as targets fail to overcome viral resistance, but multiple drugs with multiple targets, given simultaneously, are effective. The latest prostate story mandates combination chemotherapy, as has long been practiced with childhood leukemia and other hematologic malignancies.

Normal cells don't typically endure sudden, massive mutagenesis, or we'd quickly morph from one species to another. Yet recent reports suggest that while normal cells have a mechanism for inducing mutations in immunity genes so as to broaden their antibody repertoire when needed, this same mutagenic mechanism may, on rare occasions, turn against many of our other genes—itself promoting cancer.

Both Taleb's ideas and the findings of the international prostate tumor team remind us of the need to welcome intellectual complexity in our approaches to treating cancer and—as we find increasingly—in health care in general.

But in all my experience, I've never been in any accident ... of any sort worth speaking about. I have seen but one vessel in distress in all my years at sea. I never saw a wreck and never have been wrecked nor was I ever in any predicament that threatened to end in disaster of any sort.
—E.J. Smith, 1907, Captain, RMS *Titanic*

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