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A Century of Empty Promises?

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It is a sort of tradition. At the end of each year, prominent biomedical journals express their concern about the alleged successes and patent failures in explaining carcinogenesis and treating cancer. The half-full or half-empty glass metaphor applies to the usual way of perceiving success and failure. The bad news for both researchers and cancer patients here, though, is that a more realistic metaphor should indicate a 10% full and 90% empty glass. Indeed, the bold introductory sentences of reviews and papers about rare, expensive, and minimal yet unexplained successes of immunotherapy stand for 10% of such a metaphoric glass. A litany of failures in chemotherapy, alone or combined with other approaches, follows.

Reports of unforeseen incompatibilities with the dogma of Somatic Mutation Theory (SMT) also appear when dealing with carcinogenesis. A Nature commentator recently posed a rather provocative yet naive question: "If having multiple driver mutations does not make a cancer, what does?" (Naxerova 2021). This and further similar comments represent the tip of the iceberg of dissent, which has been building up in the sea of scientific and public opinion over the past two decades. More specifically, considering, "the low value of many oncological treatments that do not contribute significantly to cancer mortality reduction, but lead to unrealistic patient expectations and push even affluent societies to unsustainable health care costs," a Dutch group compellingly argued for "an urgent call to raise the bar in oncology" (Schnog *et al.* 2021). The authors critically list multiple examples of unfulfilled claims of cancer "cures" based on preliminary reports of dubious factual nature. Intriguingly, those critical comments do not offer a plausible alternative rationale to explain carcinogenesis nor propose therapeutic options. Regarding the latter, killing cancer cells has not significantly altered the bad outcomes that have been familiar to oncologists for decades.

The dominant view on carcinogenesis has relied on SMT for over a century. Its theoretical premises are the following: (1) cancer derives from a single somatic cell that has accumulated multiple DNA mutations; (2) the default state of cell proliferation in metazoa is quiescence, and (3) cancer is a cell proliferation disease caused by mutations in genes that control cell cycle and proliferation. All along, most experimental and clinical researchers have remained loyal to SMT despite the compelling evidence of its shortcomings, as noted by credible commentators. Recently, technological advances made massive DNA sequencing possible. This allowed for revealing that cells in certain cancers carry no driver mutations, while normal cells do. Some well-known researchers have reacted to such a blatant incompatibility with SMT by minimizing its relevance and refusing any correction of its course. Their *ad hoc* justifications involve proposing new epicycles to the old paradigm (Colom *et al.* 2021; Shiu & Lander 2021; McNeal *et al.* 2021).

Have we reached the tipping point? In Popper's terms, SMT has been reliably "falsified," while in Thomas Kuhn's terms, it has suffered multiple anomalies. Nevertheless, mainstream oncology stands impermeable to the emerging plausible alternative theories. It rather proposes to rely on more technology under the umbrella of the old paradigm, which means larger and more costly projects for the same failure.

When searching for explanations of this stasis, it might be timely to ask whether the salaries of those who benefit from the U.S. Government's "War on Cancer" extravagant investment, and that of their international counterparts, may have a role in it. As stated by Upton Sinclair "It is difficult to get a man to understand something, when his salary depends upon his not understanding it!"

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