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The Hallmarks of Failures in Cancer Research

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Shortly after the influential book *On the Origins of Species* (Darwin 1859) proposed a paradigmatic change on our understanding the way living beings evolve, the Scottish philosopher John Stuart Mill enunciated principles of what eventually would become a standard in evaluating scientific hypotheses. In 1869, he wrote,

> "If an instance in which the phenomenon under investigation occurs, and an instance in which it does not occur, have every circumstance save one in common, that one occurring only in the former; the circumstance in which alone the two instances differ, is the effect, or cause, or an indispensable part of the cause, of the phenomenon." (Mill 1869).

Most scientists, in particular those embracing empiricism, adopted this formula to conduct their own research and for assessing the research of others. For example, the American physicist Richard Feynman exposed his *modus operandi* and that of his peers as follows:

> "First, we guess it. (...) Then we compute the consequences of the guess, to see what, if this is right, if this law that we guessed is right, we see what it would imply. And then we compare those computation results to nature. Or we say, compare to experiment or experience. Compare it directly with observation, to see if it works. If it disagrees with experiment, it's wrong." (Feynman 2022 [1964]).

In other words, the empirical evidence favored invalidating the guessing and suggested dropping the hypothesis. Most physicists did and still do so—even those who are not empiricists. Probably, this type of intellectual detachment lays behind the much discussed "physics envy" attributed to reductionist biologists regarding physics' success as an "exact science".

In recent decades, cancer research has gone through embarrassing episodes. Despite the generous and rather extravagant amount of taxpayers' funding that it received in the last half a century, "thought leaders" and managers of those funds have little to show for it when guessing, explaining, and "curing" the disease. The constant moving of the explanatory goalposts and/or the addition of *ad hoc* alternatives have become a frustrating routine. More specifically, during the last century, cancer was considered: a genetic disease (remember Boveri, a stance still dominant today?); a parasitic disease (remember Fibiger?); a metabolic disease (remember Warburg?); an infectious disease (remember viral carcinogenesis, oncogenes?); a disease due to radiation (remember Hiroshima and Nagasaki?); an immune disease (remember McFarlane Burnet and followers?), and a combination of the above—and what not? In addition, when explanations failed, slightly modified updates of the original version were "resold" to the research community and to the public as novelties that would disentangle the cancer puzzle (most likely in the renewable next ten years). Consistently, however, these explanations were based on views claiming that cancer was a cell-based, genetic disease, caused by DNA mutations that would make the mutated cells proliferate autonomously. Such is the tenet of the Somatic Mutation Theory (SMT) and its *ad hoc* variants (see above). In fact, these are the hallmarks of the failures in cancer research. Alternative theories that explain carcinogenesis as organogenesis gone awry are seldom invoked.

Despite a lack of empirical evidence in its favor, the SMT and its successive and overlapping variants have been successfully "sold" to funding agencies as the necessary and sufficient condition for cancer to develop. As a result, research and academic institutes greatly

expanded in size and personnel. To the surprise of many molecular biologists turned cancer researchers, the enormously powerful technological advances generated by the Molecular Biology Revolution empirically documented that the single uncommon circumstance that Stuart Mill was referring to over 150 years ago did not lead to finding the somatic mutation component as the actual cause of cancers. In fact, somatic mutations in alleged cancer driver genes were found to be present both in normal and cancer cells. How this unexpected (from the SMT perspective) outcome could have been successfully managed before a critical public opinion? Thought leaders and managers who were on the record favoring the currently hegemonic SMT could have either a) reinterpreted the evidence or b) dropped the old paradigm and adopted instead alternative theories that were not at odds with the voluminous existent data. Clearly, this alternative represents a paradigmatic change of the magnitude described by (Kuhn 1962). Instead, if the first option was to be followed, then the repeated failure to validate the SMT could no longer be ignored. Dropping the failed theory, as Feynman naively advised, would generate a monumental sociological upheaval in scientific and academic circles.

Theoretical and empirical compromises as those described above tried to explain cancer for over a century. This has encouraged thought leaders to propose a new compromise, *i.e.* an *ad hoc* hybrid between the original, cell-based, and technologically driven SMT and a partner of convenience represented by the already discredited, 70-year-old, two-step initiation and promotion cancer model (Berenblum & Shubik 1947). This old-new epicycle considers driver genes' mutations as "necessary" but not sufficient, while inflammation triggered by air and other sources of pollution would act as "promoter" (Gallagher 2022). This will preserve the legitimacy of the search for more elusive driver genes and the survival of the status quo.

Who will be asked to decide what to do next? Basic and clinical cancer researchers increasingly compromised the good faith commitment of the public at large (*i.e.* taxpayers) and of young researchers (graduate students, postdocs) to foresee a bright future for science and for the lot of cancer patients. It is finally time to acknowledge that cosmetic changes will not do the job. The alternative of switching paradigms from reductionism to organicism in cancer research has become compelling. It would be sad and dangerous to our society and to science at large to admit that John Stuart Mill teaching on how to test an hypothesis has been ignored for no good reason, and that Max Planck might have been right when he concluded that,

> "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." (Planck 1950, pp. 33–34).

Let us all hope that a new generation of researchers is ready to acknowledge past conceptual failures and re-start cancer research based on reliable and evolutionarily relevant premises.

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