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Inattentional Blindness in Biology

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Our mind can trick us into ignoring the obvious if we focus too much on something in particular. This phenomenon, known as inattentional blindness, is illustrated by Simons & Chabris (1999) in their experiment, where participants are asked to count the number of passes made by players in a recorded ball game. While most viewers excel at counting the number of passes, only a minority notice a person dressed as a gorilla who is slowly walking among the players.

Scientists are not immune to inattentional blindness and, unfortunately, this blindness could cost human lives. A historical example of this blindness is the centuries-long dominance of the theory that infectious diseases were caused by miasma. This term indicated invisible vapors, detectable by their smell, and supposed to be produced by sick people, swamps, and the pools of human waste in cities. Fighting miasma by draining swamps, constructing urban sewers, and prescribing plenty of fresh air to patients led to improvements in public health, reinforcing the belief in the theory and the consequent implication to follow its prescriptions and stomp out miasma dissidents.

As we now know, miasma was a figment of scholarly imagination, which for centuries favored fiction to actual culprits, i.e., bacteria. Indeed, Marcus Varro in the 1st century BC speculated that "tiny creatures" invisible to the naked eye grow in swamps and, if swallowed or inhaled, caused disease. Girolamo Fracastoro, the physician that coined the word syphilis, furthered this idea in 1546 and named the pathogenic creatures "germs" (*seminaria*). However, evidence for the existence of "tiny creatures" was lacking until Antoni van Leeuwenhoek, using the microscopes he crafted, described unicellular organisms, including bacteria, in 1676. It took two additional centuries to reach the point when a disease could be attributed to a microorganism; indeed, in 1854 Filippo Pacini (Pacini 1866) and Joaquim Balcells i Pascual (Esteva de Sagrera 2018) independently identified the bacterium that causes cholera. Their discovery, however, was ignored for several decades because most scholars and physicians still firmly believed that infectious diseases were caused by miasma. It took the insight, energy, and public prominence of Pasteur and Koch to make them see the "gorilla" lurking in their midst.

Is this story relevant today? As human nature evolves slowly also for scientists, the possibility that we are still inattentionally blind to something even within our area of expertise is not negligible. As the story of miasma illustrates, a symptom of inattentional blindness is the persistent failure to solve a problem completely while having some success in alleviating it.

This symptom leads us to cancer research, a prospering field that has failed to noticeably reduce cancer mortality despite the unprecedented research effort and astronomical financial resources it has consumed. A recent article in *Cancer Cell* can be used as a case study. This article attempts to answer a fascinating, puzzling, and clinically relevant phenomenon, i.e., the existence of *exceptional responders* (ER), that is, "patients for

whom a complete or partial response was expected in less than 10% of similarly treated patients or whose duration of response lasted three times the published median or longer". The term "exceptional" underscores once again that the response of most cancer patients to therapy is unexceptionally poor, which gives additional urgency to finding the mechanisms underlying ER.

In search of these mechanisms, the authors assembled an unprecedented collection of ER cases (111 in total) and attempted to define what was common among them. The analysis used several approaches but, overall, was based on the somatic mutation theory of carcinogenesis (SMT), which underlies most of the current cancer research. The SMT posits that cancers are cell-based diseases caused by mutations in certain genes. After analyzing the collected data, the authors concluded that "[a] final important observation is that the majority of ER cases could not have been "solved" by analysis of DNA mutations alone, emphasizing the need for multi-platform genomic analyses of additional ER cases in the future. Such analyses may solidify, modify, or reject the hypotheses [about specific molecular mechanisms] we have proffered, arguing for an international effort to study large cohorts of these fascinating patients" (Wheeler *et al.* 2020).

This conclusion adds to the growing list of observations that the SMT fails to explain. For example, not all carcinogens cause mutations, which implies alternative mechanisms of carcinogenesis, as does the observation that some cancer cells have no detectable alleged cancer-causing mutations at all. Likewise, the causal role of mutations is also challenged by the presence of presumed carcinogenic mutations in normal tissues and benign tumors and by the fact that no known mutations or their combinations directly cause cancer. Equally puzzling for this theory are observations that normal cells transplanted into organs treated with carcinogens give rise to cancers, that mouse teratocarcinoma cells inserted in normal blastocysts can generate normal mice, that cells from a carcinoma are normalized when placed into healthy orthotopic tissues, and that many cancers can regress spontaneously.

Given this evidence, an unbiased observer may wonder whether continuing to focus on cancer genomics comes at the cost of ignoring the "gorilla" that can account for those otherwise puzzling observations. For example, the Tissue Organization Field Theory (TOFT) explains these observations by positing that the initiation and progression of cancer is due to the disruption of the normal interaction of cells and tissues, and that proliferation is the default state of all cells (Sonnenschein & Soto 2020). An increasing number of observations suggest that cancer initiation and its progression, or regression, are not primarily caused by intracellular processes but should be considered, instead, relational phenomena occurring in tissues, involving the entire organism and its environment.

If alternative theories can explain the observations at which SMT fails, why then cancer research continues to focus on a theory that has lesser explanatory power? If SMT is *the* solution for cancer, why do physicians still continue treating cancer patients with drugs that are deemed by this very theory as carcinogenic?

As past and current accounts of science suggest, answers may lie not only in the realm of data and facts, but in conceptual, social, economic, and ideological currents that influence science as a human activity and, together, make it easier to overlook "gorillas". Indeed, oncology is a profitable and growing business, with positive outcomes so negligible that they require large cohorts to detect them.

Viewing cancer as a part of an organism would help experimental and clinical cancer researchers to consider empirical evidence and the explanatory power of theories, rather than ranking them by how popular, prevailing, or remunerating these theories are. This approach may help those in this field to notice "gorillas" which may be walking around research laboratories and cancer wards in plain sight, while researchers and clinicians are busy counting and cataloguing genomic abnormalities.

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