The biological side of randomness.

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The advancement of science is possible -only- if science can be questioned.

Abstract

This is my comment to an article that was recently published by Science (see ref.1) raising several issues. In this brief note I will not address the methodological issue, as the main merit of the article is to have questioned the preventive medicine as a strategy by undermining its foundations with the randomness of disease, in this case, the cancer. To understand the scope of this refutation we must remember that the preventive strategy was developed since the introduction of the concept of risk factor, that date back to the Framingham Heart Study (FHS) started in 1948. Indeed, prior to the FHS, doctors were still engaged in the study of causation by following the established paradigm of aetiology, and had not yet focused on the concept of prevention or prophylaxis. After having metabolised the concept of risk factor for disease and having made prevention of risk factors the main strategy to fight multifactorial diseases for years, today, in a Western world that is aging, we are facing a new challenge since prevention seems to be no longer enough to cope with diseases such as cancer and, possibly, we need new strategies that we still have not. And this why? Possibly because the randomness appears ever more like the engine that drives the physical universe even if, for living organisms, we must admit several deterministic or, at least, very reproducible events since they are able to actively interact with the environment [a].

Key Words: preventive medicine, risk factors, Framingham Heart Study, randomness, deterministic, thermodynamic, organic compound, information, signaling, pattern, variability, adaptability, behavior, disease, cancer, prevention, statistics, neoplastic drift, evolution, chaos, non-linear dynamics, generative, stem cells, environment, stress, cell division, genetic program, fate.

Diseases, prevention and fate.

The main interest of the article by Tomasetti and Vogelstein (1) is not scientific but, rather, philosophical; mathematical proofs produced are the unavoidable prelude to question our scientific certainties: *we have not yet understood enough about the disease and, in particular, about cancer*. This means that, in a Western aging population, the prevention of risk factors is no longer enough and we need new ideas to inspire medical research and care. *Prevention is better than cure* was a great slogan but, when clinicians still claim to operate by making inference on the *machine of fate*, despite knowing that this machine is driven largely by randomness, well we have a problem and this is, at least in part, our ignorance of the phenomenon that requires, above all, a reflection, from an historical perspective, on the science of certainty and uncertainty (2). To broaden the view of the matter, it must be remembered that prevention is fueled by the results of scientific research which, in turn, is non a free domain but is subject to public or private funding, according to a complex and questionable interference pattern. But persuade people to adopt a certain lifestyle, which is supposed to be healthier, is a matter of public interest rather than scientific, perhaps it would

be better to let science to produce new (and more brilliant) theories keeping in mind that scientific proofs are partial, whether they are supported by observational or experimental studies, and they are likely to be flipped or changed by the advance of knowledge.

Randomness in the clinical domain.

If the study of randomness, from the mathematical point of view, is a challenge in the search of a sufficient random event, while for the physicists the scattering of protons is a true random phenomena (3), from the clinical point of view, a random event, like an unexpected disease, could have other *pseudo-random*[b] explanations related to the history of that individual patient suffering from "bad luck". Before building the *clinic of randomness*, it might be useful to consider patients not only as cases of a statistics but like mind-body unities with a psychosocial individuality and all physicians are invited to do a serious reflection on Descartes (4). When considering the series of events leading to the *neoplastic drift* they are possibly *non-linear* or *truly-random* showing a kind of evolution which reflects the changes of the environmental pressure on the individuals and their adaptive responses, following a pattern that was defined, not surprisingly, *deterministic chaos* (5). The statement of the study object of this comment that *"only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions"* is partial as the remaining two thirds attributed to "bad luck" occur exactly where the *genetic program* has planned to allocate generative and re-generative resources, namely, *stem cells*, for development and for adaptive processes in order to buffer environmental changes (6); thus, tissues that undergo the greatest environmental stress and, therefore, require a greater renewal, are the ones most exposed to the risk of developing malignancies. In such view, more suited to a pathologist, the correlation reported between the *"number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer tissue"* clearly underlies the increasing environmental pressure on biological life and the not easily predictable individual response to this kind of stress, thus the boundary between health and disease is, at least, *fuzzy* as it moves according the reciprocal interaction between phenotype and environment and each of us is a different phenotype. Buffering an environment in continuous change across the boundary between health and disease is just what living organisms are doing since about 3,500 millions of years and the results are again a matter of individual adaptability (**figure 1**).

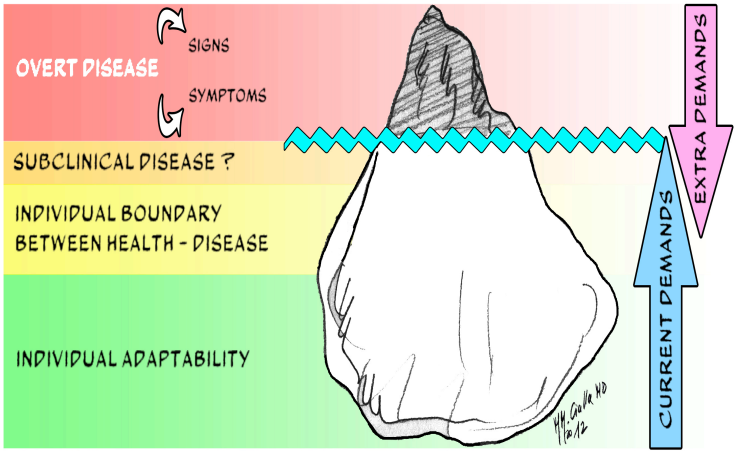

Figure 1.
Representation of the iceberg metaphor, illustrating the boundary between health as a result of individual adaptability and disease. The tip of the iceberg corresponds to overt disease; the huge part below the water line is where individual adaptability successfully buffers environmental demands; just below the surface is the grey zone of subclinical disease. Demands are defined as current or extra according to how efficiently they can be handled by the single organism.

Notes

[a]*Living organisms stand like an exception since they are able to reorganize the thermodynamic free energy from the environment into organic compounds, which are the basis for the accumulation of information, from signaling to behavior.*

[b]*It is worth to remember that there is a mathematical definition for the concept of pseudorandom processes that refers to processes that seem random but they are not since an algorithm is able to predict them. In our case the algorithm is currently still unknown.*

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