Theory in carcinogenesis and epidemiology

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How application of the principles of natural selection can lead to progress in cancer epidemiology

An argument could be made that despite the unquestionably rapid pace of scientific progress in the biological and biomedical sciences, our actual level of understanding of the mechanisms that operate in living organisms is less profound, less integrated, and less easily communicated than it should be, given the enormity of the data that have been generated. I believe that the reason for this discrepancy between the weight of facts and the breadth of our knowledge stems from a paucity of theoretical effort. In all other fields of science, theoretical and experimental work tend to progress together, each driving the other, and leading to some degree of integrated framework of understanding. The absence of a real theoretical framework for modern biology has severely hampered any attempt to make sense of all the data in an integrative manner.

Biological scientists are not as familiar with theory and its importance as are physicists, and many biomedical scientists, molecular biologists, and clinical researchers do not truly understand that theory is especially useful when the picture presented by large amounts of data seems to be overwhelmingly complex and intractable to simple analysis. Darwin and Wallace, along with many before them, collected vast amounts of data about the morphology and comparative anatomy of species. These data seem boring and trivial, when compared with the elegance of the theory of evolution by natural selection that evolved from them. Theories have the great benefit of focusing experimental work, allowing

for a much more efficient use of the laboratory than, for example, we now see. If anything, modern biology, especially molecular biology, is moving in the opposite direction, away from hypothesis to "discovery" driven science.

The paper by Vineis *et al*¹ on the application of the one grand theory of biology—natural selection—to carcinogenesis and cancer epidemiology is a creative and welcome exception to the anti-theoretical bias in biomedical science. It is not the first time that the principle of natural selection has been invoked to explain some of the more difficult aspects of cancer biology. Nowell published a classic paper in 1976² on the role of natural selection in the progression of normal cells to highly malignant, invasive, drug resistant, metastatic, and deadly tumour cells. Experimental evidence in support of this idea followed, and it is now accepted that such a selection mechanism is operative in most, if not all cancers. Mechanisms to explain how such a selective evolution can occur so quickly, including the mutator phenotype, loss of heterozygosity, and other molecular details were proposed and then supported by experimental evidence.

Natural selection is a powerful theory in many areas of biology, besides natural history and evolution of species. It is vital in understanding the patterns of infectious disease, drug resistance in bacteria, and many other areas of public health and medicine. Its application to cancer epidemiology could herald a new paradigm of epidemiological research, where data driven approaches have usually

dominated the field. Vineis *et al* provide several examples of epidemiological observations that could be explained by the application of the two main operating forces of the Darwinian theory—variation (in this case produced by somatic mutations from exposure to mutagens) followed by selection pressure, often produced by a toxic environmental exposure, that allows for selective survival of mutated clones. Perhaps the most challenging and provocative aspect of the paper is the last section on new mathematical approaches to describe the carcinogenic process. The authors introduce (possibly for the first time in a discussion of cancer modelling) concepts related to complexity and chaos theory, such as attractors and the Lotka-Volterra equations, as potentially useful approaches to allow for the analysis of carcinogenic biological processes as related to selection and competition. The Lotka-Volterra difference equations were developed to model competition between species in an ecological setting. In certain situations, these equations give chaotic, non-linear, and non-predictable results. Given what is known about the enormous complexity of the carcinogenic process, use of models such as these may be perfectly justified, and might provide the theoretical framework that is so desperately needed in this age of data overload to make real progress in the understanding of human carcinogenesis.

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REFERENCES

- 1 Vineis P, Matullo G, Manuguerra M. An evolutionary paradigm for carcinogenesis? *J Epidemiol Community Health* 2003;**57**:89–95.
- 2 Nowell PC. The clonal evolution of tumor cell populations. *Science* 1976;**194**:23–8.