

And yet another epicycle

Sir,

We have read the Commentary by Professor Henry Harris attentively and concluded, first, that we should all be thankful to Professor Harris for his unvarnished dismissal of so many of the myths (he calls them “fashions”) that the field of carcinogenesis has withstood in its history of failures. Is this a symptom of a paradigm shift in cancer research? Paradigm shifts, according to Thomas Kuhn, occur when an anomaly ceases to be just a puzzle. Early on, ad hoc adjustments are proposed. Thus, those researchers that thought that a single gene mutation was sufficient to explain carcinogenesis started to add up more gene mutations to obtain the same effect. Then, not only proliferation but also apoptosis had to be involved. Soon, angiogenesis needed to be added, and so on.

Will these revelations and the alternative offered by Professor Harris change the direction of cancer research? On the one hand, since grant review panels are still populated by those researchers who have originated and/or championed the idea that carcinogenesis is due to aneuploidy or to mutations affecting oncogenes, tumor suppressor genes, cell cycle genes, angiogenesis, or apoptosis, we seriously question the possibility of a rapid turnaround. On the other hand, Kuhn concluded that “the competition between paradigms is not the sort of battle that can be resolved by proofs,” that is, solely by the power of compelling data.⁽¹⁾ Although some of those researchers have retired or are about to do so, it is not a secret to savvy observers that most of those “pioneers” have created their own dynasties; in turn, these groups are naturally bound to maintain themselves as all well-managed bureaucracies do. In any case, we thank Professor Harris for speaking forthrightly and elegantly on what cancer researchers should finally acknowledge.

However, when Professor Harris wishes to show us where those metaphorical keys were lost, he chooses to dismiss all those cancer genes and their variants that in hindsight have not panned out and adopts instead his own alternative, but still cell-based, model. According to him, cancer is then due to mutations in genes that affect cell differentiation (“the disordered cell multiplication seen in malignant tumours must be the result of an error in differentiation”). This brings us yet to another myth: i.e. the claim that undifferentiated cells proliferate and differentiated cells do not,⁽²⁾ which perpetuates the reductionistic attitude of centering carcinogenesis at the cellular/subcellular level of organization, and invokes DNA mutations as necessary causes in carcinogenesis. This view conflates *cause* with *explanation*. If cancer is to be explained as a problem of cell differentiation, why are mutations in the DNA of genes that regulate differentiation necessary, as Professor Harris claims? Liver cells differ from those in the kidney, yet their differences are not due to genomic mutations.

In short, Professor Harris thus reverts to a cell-centered pathogenesis where proliferation is solely regulated by the differentiation status of a cell, re-enforcing the popular tautology that differentiated cells do not proliferate and cells that do not proliferate are differentiated.

Also, after over four decades of ignoring the worthy concept of *proliferation* as the default state of cells in metazoa, Professor Harris dusts up this evolutionarily relevant notion and re-claims it as his own, dating back to 1958. The record shows that he later dismissed this notion by omission and by deeds; for example, there is no mention of this issue in his 1995 book entitled “The Cells of the Body.”⁽³⁾ In fact, as we describe in our book that Professor Harris reluctantly footnotes in his Commentary, this dual attitude is comparable to that of others who, like Professor Harris, at some point in their research programs considered *proliferation* as the default state of all cells and later acknowledged, always in good faith, that inhibitors as well as “growth factors” regulate cell proliferation.⁽⁴⁾ We are alluding to F.C. Stewart, W.S. Bullough, O.H. Iversen, and probably others who must have been persuaded to balance their views by a *Zeitgeist* favoring research programs aimed at identifying an ever-increasing number of putative growth factors.

It is odd to notice that Professor Harris does not even mention that during the period he covers there has been a number of researchers that, rather than adding ad hoc adjustments, have offered alternative organicist hypotheses on carcinogenesis and buttressed them with supporting data.^(5–10) Specifically, some of us have explicitly claimed that heritable and sporadic types of cancer are *tissue-based* diseases explainable as disruptions of the reciprocal stroma/epithelium interactions that instruct histogenesis and maintain normal tissue architecture.^(4,11–13) Both in concept and in deeds, this epigenetic model stands opposite to the classical somatic mutation theory and the variant Professor Harris defends when it is due to his preferred type of mutated genes, i.e. genes that affect cell differentiation.

Summing up, as we discussed one year ago in this section of Bioessays, the somatic mutation theory, together with Professor Harris’ cell differentiation variant, *explain* cancers as cell-based diseases of the control of cell proliferation or the control of cell differentiation. In this interpretation, DNA mutations are a *sine qua non*, necessary *cause*. In contrast, the organicist theories *explain* cancers as tissue-based diseases.^(14,15) In this interpretation, the disruptions of the reciprocal interactions between cells and tissues that underlie carcinogenesis do not necessarily require mutations. For all these reasons, the organicist views provide a truly meaningful alternative to the somatic mutation theory.

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