On the Concept of Minimum Deviation in the Study of the Biochemistry of Cancer

One of the goals in cancer research is the understanding of the biochemical basis for the altered metabolic and cellular behavior of neoplastic tissue in an intact host. Historically, this major branch of cancer research can be divided in general into four overlapping periods, each characterized by a certain underlying philosophic approach (3, 16, 17).

The first period is best represented by the extensive studies of Warburg (18), who analyzed a wide variety of human and animal cancers. Many of the neoplasms so studied were advanced biologically and, in retrospect, often represented malignancies in late stages of progression (7). In such cancers, selected more or less randomly, reproducible changes in levels of glycolysis and respiration were consistently found, and these came to be recognized as biochemical hallmarks of cancerous tissue.

However, this consistency was less evident during the second period in which the transplantable malignant neoplasm, albeit of many different cell types, was the model studied. This period is best exemplified by the extensive studies of Greenstein (9), who was able to discern certain general patterns of deviation of many metabolic activities. In retrospect, it is becoming evident that this approach documented, in biochemical terms, what was already known from biologic and histologic studies, namely, that neoplastic behavior of any tissue is compatible with many different appearances and phenotypic expressions of their component cells. No single change or groups of biochemical changes were found which could be correlated with malignancy of any tissue or organ.

The third period was led by the outstanding investigators at Wisconsin, especially the Millers (12) and Potter (14), who suggested that deletions of specialized proteins or enzymes may be an important general mechanism for neoplastic transformation. Although this hypothesis has stimulated considerable work in the biochemistry of cancer and carcinogenesis, unequivocal evidence in its support has been difficult to obtain. Comparisons between many different transplantable tumors and their tissues of origin have failed to uncover completely reproducible enzymatic alterations which could be correlated with the biologic properties of the neoplasms. Also, the discovery of an increasing number of neoplasms which seem to have acquired new properties, e.g., hormone production (11), antigens (10), etc., not apparently found in the homologous normal adult tissue, tends to argue against this concept.

In the most recent phase, developed in the past several years, emphasis in the study of the biochemistry of cancer has been shifted increasingly to the comparative analysis of a series of neoplasms derived from a single organ or tissue. The concentration upon neoplasms of one cell type, showing varying degrees of differentiation, is based on the sound philosophic premise that the neoplasm with the greatest resemblance to the normal cell of origin is most likely to show the least deviation and therefore is the simplest cancer model. This principle, enunciated in its clearest form by Potter (15–17), has encouraged the rapid accumulation of a variety of “minimal deviation” hepatomas (13).

Thus, the emphasis in the biochemical analysis of cancer has been moving successively to neoplasms of less advanced stages of progression. This, in the opinion of this author, is a very important conceptual advance which, if carried to its logical conclusion, may lead to a major new insight into the cellular metabolic organizational patterns associated with neoplasia and to the development of testable hypotheses. However, it is proposed that the criteria for selection of “minimal deviation” neoplasms must be changed for this new conceptual approach to prove maximally profitable.

It is now well documented that the neoplastic transformation in an intact host is most probably not a single event, as was once believed (1), but rather is a multistep process in which cells and tissues progressively manifest the biologic properties which characterize a highly malignant cancer (2, 7, 8). The stepwise nature of this transformation is apparent in many systems including chemical carcinogenesis (2, 5, 6), viral induced mammary cancer in mice (4), radiation or hormone-induced neoplasms (8), and different human cancers. New cell populations which have acquired properties of growth without invasion or metastasis or which show only histologic aberrations (carcinoma-in-situ), are recognized in many instances as precursors of a fully malignant neoplasm. The existence of such groups of cells, showing only some of the characteristics of the final cancer, point to the conclusion that any neoplasm showing invasion and metastasis is already too advanced to be considered “minimally deviated.” It is most likely that each of the overall biologic properties of a malignant neoplasm is a reflection of several or many biochemical alterations from the normal homologous tissue. If this assumption is valid, then one must conclude that no neoplasm characterized by growth, invasion, and metastasis is minimally deviated, regardless of its state of differentiation.

It becomes apparent, therefore, that the present criteria for selection of a “minimal deviation system” for biochemical analysis must be biologic rather than biochemical. Cell populations for initial study should be chosen which show only single biologic aberrations such as growth control without the added complexities inherent in the acquisition of the properties of invasion and metastasis. Insight obtained from such bodies could then be used in the analysis of further stages of neoplastic progression culminating in the fully developed malignant process.

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Some information concerning possible model systems is already available. The dependent hormone-secreting tumors developed by Furth (8), the hyperplastic nodule in the mammary gland studied by DeOme et al. (4), and the hyperplastic nodule in the liver of the rat induced with different carcinogens (5, 6) offer three such possibilities. Each of these represent readily identifiable new cell populations which have acquired growth characteristics different from the parent tissue and which appear to be precursors of malignant neoplasms.

Considering the magnitude of the human effort and resources now being used in the important study of cancer biochemistry, it behooves us to make the most careful selection of model systems. Hopefully, these remarks will stimulate further interest in fostering discussion which may lead to the maximum exploitation of the important concept of "minimal deviation."

References


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