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Farber E. Ethionine carcinogenesis. *Advan. Cancer Res.* 7:383-474, 1963.
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The review focussed on mechanisms of ethionine carcinogenesis. Effects of this methionine ethyl analogue in prokaryotes and eukaryotes, similarities in the carcinogenic process between the steps with ethionine and other hepatocarcinogens, and possible cellular metabolic bases for some steps were included. [The *SCI*® indicates that this manuscript has been cited in over 405 publications.]

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During medical school in Toronto, and subsequently in graduate school in Berkeley, I became increasingly interested in studying the biochemical basis for the development of cellular and tissue changes in disease, with special emphasis on acute cell injury. The development of the concept of metabolic antagonism late in the 1930s and the availability of a few antagonists, including ethionine, led naturally to the study (during my graduate work under D.M. Greenberg and H. Tarver in the immediate postwar period) of the metabolic disturbance induced in animals by ethionine. These studies gave us new insights into the quantitative modulations of some biochemical networks relating to methionine, such as an imbalance between the synthesis of S-adenosylmethionine and its utilization as a methyl donor.[1] This orientation became useful in later studies on liver carcinogenesis with ethionine, since it highlighted the concept that quantitative variations in normal metabolic pathways may play an essential role in the development of disease.

This viewpoint was then, and today still is, in apparent conflict with the dominant paradigm. The field is guided largely by the thesis that cancer is a direct consequence of "relatively simple," structural, "abnormal" changes in DNA, RNA, and protein components of cells induced by chemicals, radiation, or viruses. All steps in cancer development are viewed as abnormal or pathological (in the etymological sense), relating somehow to mutations.

Research on the genesis of cancer and other diseases with ethionine remains a challenge to this dominant paradigm. The current availability of exciting new technological tools for gene and genetic analysis, including proximate and ultimate gene products, makes it very attractive to explore anew a further level of biochemistry and molecular biology through the study of ethionine carcinogenesis. The study of modulations of gene expression and phenotypic behaviour of target cells, coupled with the persistent validity of the thesis that the metabolism of ethionine follows closely the natural enzymatic pathways for the metabolism of methionine, should enable an alternative, much more physiological[2-6] approach to the mechanistic analysis of how a cancer develops and how the process might be modulated so as to prevent cancer in humans by its manipulation.

I believe that the interest shown in this review is due to at least two considerations: (1) the different perspective that ethionine carcinogenesis generates in scientists interested in the pathogenesis of cancer, and (2) the continuing usefulness of metabolic antagonists, especially of important metabolites such as methionine in the analysis of metabolic control and cell regulation. The obvious relevance of ethionine to methionine and the growing realization of the key role that methionine plays in fundamental cellular metabolism including DNA replication, gene expression, and membrane integrity make the study of ethionine carcinogenesis of special interest. Also, the "rediscovery" of choline deficiency as a cause of cancer[4] has reopened interest in disturbances in the metabolism of methionine and choline as a basis for the altered gene expression during cancer development. Comparisons between the many steps in cancer development with a choline-deficient diet and with ethionine may prove to be a profitable new area in which the roles of diet and nutrition in the pathogenesis of cancer can be explored.

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4. **Farber E & Sarma D S R.** Biology of disease: hepatocarcinogenesis: a dynamic cellular perspective. *Lab. Invest.* 56:4-22, 1987.
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