

## AN INTEGRATED CONCEPT OF CARCINOGENIC- ANTICARCINOGENIC ACTION<sup>1</sup>

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Recently, a theory has been formulated (Kovacic, 1960a) which presents a unified picture of the initial step of carcinogenesis, applicable to a wide variety of carcinogens. According to the proposal, cancer originates in the action of an agent, derived from either an artificial carcinogen or a spontaneous process, which directly or indirectly generates hydrogen peroxide in abnormally high concentration. Possible routes whereby such a situation might arise include the inhibition of catalase, catalytic conversion of oxygen to hydrogen peroxide, and decomposition of body water by high energy radiation. Attack by hydrogen peroxide upon the cellular constituents is considered (Kovacic, 1960b) the subsequent stage in the sequence of reactions leading to the cancerous condition. This approach emphasizes the importance of the hydrogen peroxide hypothesis which had been advanced previously by various investigators without wide acceptance. Moreover, for the first time a reasonable theory is provided which correlates in a specific manner a wide array of structurally different carcinogens in relation to the initiation of cancer.

This communication presents an integrated view of carcinogenic-anticarcinogenic action based primarily upon these theoretical considerations, in addition to certain previously reported concepts and investigations.

Three types of cellular response (Haddow, 1947) appear likely in connection with increased levels of hydrogen peroxide. Cellular changes induced by slight increases could be overcome readily in the direction of normal cell regeneration. Exceptionally high concentrations would result in destruction of the cell as a reproductive entity. However, intermediate levels might well effect reversion to a simpler state capable of growth and division—the condition designated as malignancy.

It is likely that the cancer cell is susceptible to attack by a number of different routes. Certain antagonistic agents appear to act as antimetabolites; this category will not be treated in this communication. Anticarcinogens, at least those discussed, will be considered as functioning by either (1) increasing hydrogen peroxide concentration or (2) eliminating excess hydrogen peroxide.

### *Anticarcinogenic Action by an Increase in Hydrogen Peroxide Concentration*

Let us first briefly discuss the mechanism which is proposed (Kovacic, 1960a) for the initiation of cancer, the unifying aspect being the generation of hydrogen

<sup>1</sup>This paper was presented at The Ohio Academy of Science meeting in Columbus, Ohio, on April 17, 1959.

peroxide. A possible route advanced in the case of aromatic hydrocarbons, aromatic amines, phenols, and azobenzenes entails the conversion of oxygen to hydrogen peroxide through the catalytic action of a metabolite such as an *o*-quinone or a quinonimine. As a more preferred alternative, increases in hydrogen peroxide are considered to result from catalase inhibition by reaction of the carcinogen with enzyme protein accompanied by coordination with iron. Tumor-inducing agents placed in this category include urethan, nitrogen mustards, ethylenimines, ethylene oxides, sulfonic acid esters of diols and *o*-aminophenols, as well as *o*-quinones—a class not yet reported to be carcinogenic. Finally, high energy radiation is known to generate hydrogen peroxide by decomposition of water.

A baffling paradox of oncology exists in the demonstration (Haddow, 1935; Haddow et al., 1948; Greenstein, 1954) that almost all of these same compounds or types of compounds are anticarcinogenic. If the premise is valid that these agents induce cancer by generating excessive amounts of hydrogen peroxide, it may well be that their anticarcinogenic action also is intimately related to the peroxide-forming property. Should this be true, the paradox would be resolved. How might it be possible for increased concentrations of hydrogen peroxide both to induce and combat cancer? An essential component of the interpretation is the thesis advanced by Holman (1956) that “. . . malignant cells—which are already deficient in catalase and abnormally sensitive to oxygen—are so easily killed by overoxidation. . . .” Support for this conclusion was provided by the demonstrated ability of hydrogen peroxide (Hollcroft and Lorenz, 1952; Makino and Tanaka, 1955; Worrall, 1956; Holman, 1957) to destroy cancerous tissue selectively. It is interesting that fetal liver is similar to hepatoma in its extremely low catalase content (Greenstein, 1954) and that agents which are antagonistic to cancer also damage (Skipper, Bennett and Wheeler, 1952) the most actively dividing normal cells. Consistent with the exposition presented thus far is the large reduction (Haddow et al., 1948) in the inhibitory effects of anticarcinogens by use of a high protein diet, as well as the anticancer action (Griffin, Clayton and Baumann, 1949) of the same type of diet, presumably by competition of diet protein with catalase protein for combination with the carcinogen-anticarcinogen.

Since many anticarcinogens also induce cancer, the anticancer property of hydrogen peroxide can be taken as an indication that it may also be carcinogenic. It is significant that hydrogen peroxide is effective in producing melanotic tumors in *Drosophila melanogaster* (Glass and Plaine, 1953; Plaine, 1955a, 1955b; Plaine and Glass, 1955). Similarly, inhibition of neoplasia by 9,10-phenanthrenequinone (Powell, 1951) supports the prediction that *o*-quinones will be added to the list of carcinogenic agents.

Chemotherapy with these various types of compounds, as well as with ionizing radiation, has in general been disappointing—a story of relapse and limited applicability. In light of the theoretical interpretations, this would indicate that increased concentrations of hydrogen peroxide are not completely effective due perhaps to the survival of resistant strains of cancer cells, or else to the generation by peroxide of new malignant cells as the established growths are eliminated. It should follow from this same reasoning that initiation of cancer by hydrogen peroxide would involve a certain degree of simultaneous inhibition. In fact, a number of investigators have observed precisely this type of refractory condition on application of carcinogens (Haddow et al., 1948; see Vesselinovitch, 1958). Numerous other factors involving high degrees of specificity would also be expected to play a role in the carcinogen-anticarcinogen balance.

#### *Anticarcinogenic Action by Elimination of Excess Hydrogen Peroxide*

On the basis of the hydrogen peroxide hypothesis, compounds capable of combining readily with hydrogen peroxide or its derived radicals would be classified

as potential cancer preventives. Substances reported as anticarcinogens (Greenstein, 1954; Skipper and Bennett, 1958) which may well function in this manner are mercaptans, maleic acid and aldehydes. Once the neoplastic condition is established, compounds in this category would act only to prevent the further generation of cancerous cells from normal ones. It should be pointed out that these substances or their metabolites can also be included in the alternative proposal which appears to be of wider scope.

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