Heidelberger C. Chemical carcinogenesis. *Annu. Rev. Biochem.* 44:79-121, 1975. [McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI]

Chemical carcinogenesis was reviewed from the perspective of a biochemist. Emphasis was on epidemiological evidence that chemicals in our environment are a major cause of human cancer; that most carcinogens require metabolic activation; and that new cell culture model systems were evolving. The most plausible mechanisms were emphasized. [The *SCI*® indicates that this paper has been cited over 610 times since 1975.]

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December 10, 1981

"It was mostly a matter of timing. *Annual Review of Biochemistry* has had its coterie of faithful readers over the decades, and the subject of chemical carcinogenesis had not been reviewed in that publication since 1959—and has not been since my 1975 review.

"The earlier review was written by my friends and colleagues Elizabeth and James Miller at the McArdle Laboratory for Cancer Research, University of Wisconsin.[1] I was fortunate to have spent many years in that laboratory, which, then and now, is considered to be one of the leading centers in the world for research in chemical carcinogenesis.

"In 1974, when I was invited to write the review, the field had undergone a number of exciting developments that clearly established the great importance of chemical carcinogenesis in the causation of human cancer and that unraveled some of the tangled complexities of mechanisms of action. These advances were recognized by many cancer researchers, but had not yet penetrated the consciousness of most biochemists.

"The first of these developments involved the increased recognition by epidemiologists that chemicals in our external and internal environments constitute a major cause of human cancer.[2] Since epidemiologists till the soil of an apparently nonbiochemical universe, I attempted to point out the importance and relevance of their observations and ever-increasing evidence.

"The second major development was the concept originated by the Millers[3] that most chemical carcinogens were not active *per se*, but required metabolic activation by cytochrome P450 monooxygenases to chemically reactive electrophiles. In my laboratory we produced the first experimental evidence that arene oxides are the activated form of polycyclic aromatic hydrocarbons.[4] My review in 1975 appeared to stimulate many 'pure' biochemists to conduct important research in this burgeoning field. It was Ames's recognition of the need for metabolic activation, which he supplied by suitably fortified liver homogenates to *Salmonella typhimurium*, that made his widely used test possible.[5] I reviewed the state of knowledge of the metabolic activation of several chemical classes of carcinogens.

"Berwald and Sachs[6] and my laboratory[7] had been the pioneers in developing model systems whereby normal rodent cells on treatment by chemical carcinogens underwent oncogenic transformation, and the implications and promises of this approach were called to the biochemists' attention. Finally, I reviewed the then status of mechanisms of action of chemical carcinogens with emphasis on somatic mutations *vs.* epigenetic mechanisms.

"I believe that the enduring popularity of the review stems from the breadth of perspectives and topics that I emphasized, which are still relevant today. Although I have received my share of honors and awards, these I believe were for my contributions to research and not for this review."

1. **Miller E C & Miller J A.** Biochemistry of carcinogenesis. *Annu. Rev. Biochem.* 28:291-320, 1959.
2. **Higginson J & Muir C S.** Epidemiology. (Holland J F & Frei E, III, eds.) *Cancer medicine.* Philadelphia: Lea and Febiger, 1973. p. 241-306.
3. **Miller E C & Miller J A.** Biochemical mechanisms of chemical carcinogenesis. (Busch H, ed.) *Molecular biology of cancer.* New York: Academic Press, 1974. p. 377-402.
4. **Grover P L, Sims P, Huberman E, Marquardt H, Kuroki T & Heidelberger C.** In vitro transformation of rodent cells by K-region derivatives of polycyclic hydrocarbons. *Proc. Nat. Acad. Sci. US* 68:1089-101, 1971.
5. **Ames B N, Durston W E, Yamasaki E & Lee F D.** Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection. *Proc. Nat. Acad. Sci. US* 70:2281-5, 1973.
6. **Berwald Y & Sachs L.** In vitro transformation of normal cells to tumor cells by carcinogenic hydrocarbons. *J. Nat. Cancer Inst.* 35:641-61, 1965.
7. **Chen T T & Heidelberger C.** Quantitative studies on the malignant transformation of mouse prostate cells by carcinogenic hydrocarbons in vitro. *Int. J. Cancer* 4:166-78, 1969.