CC/NUMBER 44
NOVEMBER 2, 1981

This Week's Citation Classic

Miller J A. Carcinogenesis by chemicals: an overview—G.H.A. Clowes Memorial Lecture. *Cancer Res.* **30**:559-76, 1970. [McArdle Lab. for Cancer Res., Univ. Wisconsin Med. Ctr., Madison, WI]

Chemical carcinogens comprise a wide variety of organic and inorganic compounds that share no common structural features. Recent **work** indicates **that** most, if not all, chemical carcinogens are, or are metabolized to, ultimate carcinogenic reactive and mutagenic electrophiles that bind covalently to informational macromolecules involved in the initiation of carcinogenesis by these agents. [The ***SCI***® indicates that this paper has been cited over 1,100 times since 1970.]

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September 9, 1981

"G.H.A. Clowes was director of research at Eli Lilly and Company for many years. He was a founder of the American Association for Cancer Research in 1907 and an early investigator of normal and malignant growth. The Clowes Memorial Lectureship Award, sponsored by Eli Lilly and Company, is awarded annually by the American Association for Cancer Research. The honor of being the ninth lecturer in this series is one that I share fully with my wife and co-worker, Elizabeth Cavert Miller. Our work together forms the greater part of this review. We owe very much to our many collaborators over the years, and especially to Harold P. Rusch, who founded and was director of the McArdle Laboratory for Cancer Research for 33 years. His selfless work established a stable, stimulating, and productive research environment at the McArdle Laboratory.

"In this Clowes Lecture I reviewed research on the molecular mechanisms of chemical carcinogenesis, especially for the decade prior to 1969, the year of the award. This decade was particularly exciting to Elizabeth and me for it encompassed our finding of the first proximate carcinogenic metabolite, N-hydroxy-2-acetylaminofluorene,[1] and our realization, conceptually and experimentally, that this and many other carcinogens are converted metabolically to electrophilic ultimate mutagenic carcinogens.[2-3] Thus it appears that most, if not all, chemical carcinogens are, or are converted *in vivo* to, strong electrophiles as ultimate reactive and mutagenic carcinogens. This finding explains the great structural variety of chemical carcinogens and the nature of the covalent binding *in vivo* of residues of chemical carcinogens to DNA, RNA, and proteins, especially in target tissues. Much work in many laboratories in the past decade has extended these concepts to a wide range of synthetic and naturally occurring chemical carcinogens.[4]

"We were surprised that so many reprints of this review were requested by investigators in such a wide range of disciplines. This probably resulted in part from the increased concern and interest about chemical carcinogens in the environment and their control in modern life. Chemical carcinogens had, in a sense, 'arrived.' We well remember how lonely a field chemical carcinogenesis in the US was in our early research years."

1. E C Miller, Miller J A & Hartmann H A. N-hydroxy-2-acetylaminofluorene: a metabolite of 2-acetylaminofluorene with increased carcinogenic activity in the rat. *Cancer Res.* 21:815-24, 1961. [Citation Classic. *Current Contents/Life Sciences* 22(27): 14, 2 July 1979.]
2. Miller J A & Miller E C. Metabolic activation of carcinogenic aromatic amines and amides via N-hydroxylation and N-hydroxyesterification and its relationship to ultimate carcinogens as electrophilic reactsnts. (Bergmann E D & Pullman B. eds.) *The Jerusalem symposia on quantum chemistry and biochemistry. Physiochemical mechanisms of carcinogenesis.* Jerusalem: Israel Academy of Sciences and Humanities. 1969. Vol. 1. p. 237-61.
3. Maher V M, Miller E C, Miller J A & Szybakkl W. Mutations and decreases in density of transforming DNA produced by derivatives of the carcinogens 2-acetylaminofluorene and N-methyt-4-aminoazobenzene. *Mol. Pharmacol* 4:411-26. 1968.
4. Millcr E C. Some current perspectives on chemical carcinogcnesis in humans and experimental animals: presidential address. *Cancer Res* 38:1479-9b. 1978.