

This Week's Citation Classic

Wheeler G P. Studies related to the mechanisms of action of cytotoxic alkylating agents: a review. *Cancer Res.* **22**:651-88, 1962. [Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, AL]

The purpose of this review was to present information from the published literature that related to the chemical and biochemical modes of action of five types of cytotoxic alkylating agents —mustards, ethyleneimines, sulfonic esters, epoxides, and N-alkyl-N-nitrosoureas. This information fell into the following categories: distribution and fate of the agents; effects upon glycolysis, respiration, and related processes; reaction with macromolecules; effects upon the properties and functioning of macromolecules; and antimitotic, cytologic, and mutagenic effects. [The SCI[®] indicates that this paper has been cited over 260 times since 1962.]

Glynn P. Wheeler
Kettering-Meyer Laboratory
Southern Research Institute
P.O. Box 3307-A
Birmingham, AL 35255

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"The initial recognition of the potential use of alkylating agents as anticancer agents arose from studies of the biological, toxicological, pharmacological, and biochemical studies of the chemical warfare agents, the nitrogen mustards, during World War II. F.S. Philips reviewed these studies and others that were reported prior to 1950,¹ and A. Gilman reminisced about the first test of these agents as anticancer agents.² After the end of hostilities, C.P. Rhoads recruited some men who had been with him in the Chemical Corps and National Defense Research Council (Philips, DA. Karnofsky, and C.C. Stock) to join him at Sloan Kettering institute for Cancer Research, where they continued their studies of cancer chemotherapy. Another member of the Chemical Corps team, H.E. Skipper, joined the staff of the newly founded Southern Research Institute, where he also initiated studies of cancer chemotherapy. The con-

tinuing interest of the Chemical Corps in the mustards and Skipper's experience in conducting field tests with them during the war resulted in the Corps contracting Southern Research Institute in the early 1950s to study further the chemistry and biochemistry of these agents. It was at this point that I, as a member of the biochemistry division under the direction of Skipper, became involved in studies of the biological alkylating agents.

"By the 1960s, many studies on the nitrogen mustards had been carried out in many laboratories, and several other types of alkylating agents had been found to have beneficial activity against experimental and clinical cancer. Many reports of the research on these agents had been published, but the reports were dispersed among many scientific journals. I was invited by the Cancer Chemotherapy National Service Center, with the concurrence of Skipper, to write a review article that would consolidate available information relating to the mechanisms of action of these agents. The above cited review was the product. The breadth of interest in the agents was reflected in the fact that we received 310 requests for reprints from persons in 35 states in this country and 228 requests from persons in 31 other countries. These figures and the number of citations to the article during subsequent years indicate that it did indeed fulfill the need for an updated, broad review. The fact that it was published in a widely circulated journal made it readily available to interested investigators.

"In the same year that the above review was published, a book³ that covered much of the same material and covered some of it in much greater detail was published. During subsequent years a number of other authors have written updated reviews of work on these agents that supplement and complement the other reviews⁴

"it is an inherent property of reviews that they become obsolete. Although the facts they report endure, the interpretations of those facts must be altered or eliminated as new facts and understanding arise. Nevertheless, the older reviews evidently retain some lasting value, as this review is still occasionally cited in the current literature."

1. Philips F S. Recent contributions to the pharmacology of bis(2-haloethyl) amines and sulfides. *Pharmacol. Rev.* **2**:281-323, 1950.
2. Gilman A. The initial clinical trial of nitrogen mustard. *Amer. J. Surg.* **105**:574-8, 1963.
3. ROM W C J. *Biological alkylating agents*. London: Butterworths. 1962. 232 p.
4. Sartorelli A C & Johns D G, eds. *Antineoplastic and immunosuppressive agents*. Berlin: Springer-Verlag. 1975. Part II. Section C. p. 1-84.