Chapter 3

The Millers and Chemical Carcinogenesis

James A. Miller and Elizabeth C. Miller discovered and developed the important unifying concept that most carcinogenic and mutagenic chemicals are not carcinogenic or mutagenic \textit{per se} but that these compounds must undergo metabolism to reactive electrophilic metabolites that exert their effects by covalently binding to critical sites on cellular macromolecules (DNA, RNA, and protein). James and Elizabeth Miller were the first to point out that “as a general class, chemical carcinogens would appear to be potential mutagens, and the mutagenicity of a chemical carcinogen in a given system will depend on its extent of conversion to electrophilic reactive form(s) and on the access of these active form(s) to the genetic material in the mutagenicity system under study.” These discoveries and novel concepts initiated a new era of modern toxicology and were the basis of (1) rapid mutagenicity tests (the Ames test and others) for the screening of potential human carcinogens, (2) research on chemically induced mutations in protooncogenes and tumor suppressor genes, (3) large person-to-person differences in the sensitivity of people to environmental carcinogens (intraindividual differences in the metabolism of carcinogens to their active forms), (4) formation of macromolecular adducts as indicators of cancer risk in molecular epidemiology, and (5) international laws regulating carcinogens in the diet and the environment.


Carcinogens and Metabolism

What kind of research did the Millers do? The epigraph above is a synopsis of the lifetime investigations of Elizabeth C. and James A. Miller. That synopsis is from an absolutely sterling source—The National Academy of Sciences of the United States. Thus, this chapter is unnecessary if the words of the National Academy are read carefully. However, most people would want more than an extremely brief summary of two lifetimes of research and this chapter is written for “most people”.

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This chapter begins with the carcinogenesis studies of the Millers. It seems to me that mutation of proto-oncogenes and tumor suppressor genes (epigraph, number 2) is entirely within the main thesis of the Miller laboratory—thus, proto-oncogenes and tumor suppressor genes are also considered in this chapter. The following chapter discusses the Millers’ remarkably serendipitous findings in the related areas that evolved from their work (epigraph, numbers 1 and 3 through 5).

Elizabeth and James were superbly trained in biochemistry as undergraduates at the University of Minnesota (Chapter Six) and the University of Pittsburgh (Chapter Seven) respectively, and as graduate students working for their Ph.D. degrees at the University of Wisconsin-Madison. They shared an abiding interest in cancer research in general and a special interest in how chemicals cause cancer. The McArdle Laboratory for Cancer Research (Figure 3.1) and its director from 1946 to 1972, Harold P. Rusch,1 afforded the Millers “steadfast support and encouragement”2 that nurtured their best efforts. It was not all that common in those early days for a laboratory and its director to support both husband and wife of a collaborating couple3—however, Rusch's confidence in the Millers was clearly not misplaced as evidenced by their subsequent collaboration with Rusch and with their major professor, Carl Baumann. The Millers, Rusch and Baumann teamed in studies on the effect of diet on the cancer-causing competence of the aminoazo dyes.4

The research of the Millers is sometimes presented in textbooks and reviews without attribution. This lack of attribution to the Millers is certainly not motivated by the wish to minimize their contributions. Rather, failure to cite the work of Elizabeth and James is simply an acknowledgement of the significance and universal acceptance of their scientific contributions—their studies have become an essential doctrine of chemical carcinogenesis. It is not necessary

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1 Harold Paul Rusch was born in 1908 and died in 1988. He received his M.D. degree from the University of Wisconsin in 1933. He was the author of Something Attempted, Something done: A Personal History of Cancer Research at the University of Wisconsin, 1934–1978. Madison: Wisconsin Medical Alumni Association, 1984.


3 An Administrative Procedure at the University of Minnesota, effective 2009, provides guidance for conducting a “Spousal/Partner No-search Hire”. The presence of University procedures for such hires speaks to the fact that they are no longer rare.

4 Studies subsequently showed that metabolism of a carcinogen may be influenced by a vitamin or other dietary factors, see: Brown, R.R., J.A. Miller, E.C. Miller. 1954. The metabolism of methylated aminoazo dyes. IV. Dietary factors enhancing demethylation in vitro. Journal of Biological Chemistry 209:211–222.