

Side by side: The work of Elizabeth and James Miller

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In the late 1940s and early '50s, a husband-and-wife team at the University of Wisconsin–Madison (UW) changed the course of cancer research. In a series of six papers published in *The Journal of Biological Chemistry* (JBC) (1–6), James and Elizabeth Miller showed that cancer-causing chemicals, known as carcinogens, had to be metabolized and undergo enzymatic transformation in order to cause cancer. The first evidence that metabolized carcinogens can modify tissue components, such as nucleic acids and proteins, came from this work.

“They were pioneers in what is now the basis of modern molecular carcinogenesis, in which tumors result from mutations in DNA,” says Young-Joon Surh, a director in the Tumor Microenvironment Research Center at Seoul National University’s College of Pharmacy. Surh was a graduate student with the Millers in the late 1980s.

Betty and Jim, as they were known to friends, met while pursuing their doctorates at UW. Jim was a teaching assistant in one of Betty’s labs. Betty was engaged at the time, but Jim won her over. They wed in 1942. Soon after graduating, both began work at UW’s newly formed McArdle Laboratory for Cancer Research. “I think they were happy just to be able to have two jobs together,” says Fred Guengerich, a biochemist at Vanderbilt University and deputy editor of JBC.

The Millers worked side-by-side in the lab and in their shared office. At the time, not much was known about how carcinogens cause cancer. The Millers took a biochemical approach. Norman Drinkwater, a professor of oncology at the McArdle Center and a former graduate student of the Millers, recalls that Jim was the hardcore chemist, while Betty focused on the biology; together, he says, “they were able to accomplish really great things.”

In a 1947 jointly authored paper, the Millers provided the first evidence that carcinogens could bind covalently to tissue macromolecules. They then set out to determine what happens to these chemicals once they’re inside an animal that allows them to bind to tissue macromolecules.

Jim published a series of studies between 1948 and 1954; Betty contributed to the papers published in 1952 and 1954. They elucidated the pathway by which the carcinogen 4-dimethylaminoazobenzene is metabolized to give rise to a product that can bind to proteins.

Today, cancer researchers measure covalent binding using radioactive chemical carcinogens. Back in the 1940s, that and other more sophisticated techniques, such as mass spectrometry, nuclear magnetic resonance, and high-performance liquid chromatography, were not available. The Millers used an aminoazo dye, which developed a pink color when it bound to a



Figure 1. Elizabeth and James Miller were rarely apart while working at the McArdle Laboratory for Cancer Research.

protein. Using a simple bench-top spectrophotometer, they quantified the extent of the covalent binding.

“In the 1940s, their work on metabolic activation of chemical carcinogens was totally new, because, at the time, many scientists believed that most foreign compounds, including carcinogens, were detoxicated by strong metabolizing enzymes,” says Surh.

In Drinkwater’s view, the biggest contribution from this series of JBC papers was the revelation that most carcinogens must be metabolized in order to produce the reactive forms that bind to nucleic acids and cause mutations, a fundamental tenet of cancer biology.

Their discovery that, after metabolism, carcinogens bind covalently to protein and DNA helped to explain why chemicals that cause cancer also cause mutations. “This really brought mutations and cancer together in a way that had not been appreciated,” Guengerich says. “They worked pretty much their whole careers in this general area, and their work has shaped the field.”

Drinkwater emphasizes that the connection between carcinogens being metabolized and binding to nucleic acids is the cornerstone of the Millers’ work. “Much of their subsequent work was related to showing that the same process was critical for cancer induction by a whole variety of chemicals,” he says.

Fred Guengerich at Vanderbilt University nominated this series as a Classic.
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“So, in fact, that pathway really is the common thread that links virtually all chemical carcinogens.”

The Millers worked side-by-side until Betty died of kidney cancer in 1987. Jim, who went on to remarry (another scientific colleague), continued to run a lab until the late 1990s and passed away in 2000.

Betty and Jim’s work, which Surh calls the basis of modern cancer research, has had a lasting impact. “After scientists discovered oncogenes in the late 1970s and early 1980s, the Millers’ work has been revisited,” he says. “(T)hey were, in really important ways, so complementary,” Drinkwater says. “Together, they were just phenomenal.”

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