ORNL's Bill Russell: Of mice and mutagens

(As published in *The Oak Ridger's Historically Speaking* column on October 21, 2013)

Last week Carolyn Krause brought us an excellent synopsis of Lee Russell's oral history from the archives of the Center for Oak Ridge Oral History. This article also relies on the oral history of Lee Russell and also recalls some information from the Oak Ridge National Laboratory Review which Carolyn edited for 25 years. Enjoy!

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In October 1947, as the Russells awaited their FBI clearances before assuming their new jobs in Oak Ridge, a fire in a peat bog near Bar Harbor, Maine, broke out of control. It destroyed much of Jackson Laboratory, where William Lawson Russell had worked for 10 years. The British-born geneticist lost his records, published data, and special strains of mice he had bred for his experiments.

Bill and his new wife Liane (disguised as a boy because women were banned from the fire line) joined volunteer firefighters in battling the blaze. The disaster forced Bill to rebuild his career from scratch while Lee started hers in the new Biology Division of what became Oak Ridge National Laboratory.

Lee met Bill when she was a college student in his summer school at Jackson Laboratory, and he persuaded her to pursue a doctorate in genetics rather than become a medical doctor. He took a job at ORNL because it was the only lab to give Lee a job.

In the Biology Division at the Y-12 Plant, Bill designed mouse cages, food containers, racks, bottle-washing and cage-washing devices for the colony the Russells started with mice obtained from a local veterinarian. By the time Bill retired in the 1980s, the colony had grown to tens of thousands of mice. And he had been named ORNL's first corporate fellow.

Bill's greatest interest as a researcher at the Jackson Laboratory, Lee told Steve Stow 10 years ago in an oral history interview, was to find ways to gauge the relative effects of environmental and hereditary factors on genetic variability.

Lee developed a spot test to indicate that a gene in an embryo's spinal cells had been altered (mutated) by radiation to which the mother mouse had been exposed. "If you were expecting an all-black mouse," Lee said, "the newborn mouse might end up with a spot that's light gray or brown, depending on which gene you mutated."

Bill needed a technique for comparing in mice the genetic damage resulting from different types of radiation (gamma and X rays, alpha and beta particles, neutrons), radiation administered very quickly or spread out in time, and radiation delivered to body cells and reproductive cells—the most important variable of all in mutation rates.

So, he developed the "specific locus test" to determine the rate of gene mutations in mice. He selected seven genes at specific loci, or points, in the mouse chromosomes. Six genes determined coat color; the seventh, ear size.

"We looked to see whether radiation could mutate genes that had mutated spontaneously in the past," Lee said. Using 85,000 mice in 1951, Bill was the first to measure a radiation-induced mutation rate in a mammal. He found that the mutation rate in the mouse was higher than that in the fruit fly. As a result, the permissible level for worker exposure to radiation was lowered to one-third of the level set on the basis of fruit fly findings.

Committees the Russells later served on were being formed to recommend radiation levels that were safe for workers and the public. Exposures to radiation were a concern because of the use of X-rays and radioisotopes for medical diagnosis and treatment, tests of nuclear weapons, and operation of nuclear power plants.

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The Russells found that the reproductive cells of irradiated male and female mice had different mutation rates. Working with Elizabeth Kelly, they discovered in 1958 that the mutation rate in mice exposed to chronic radiation (600 R over six weeks) was one-third to one-fourth the mutation rate in mice exposed to acute radiation (600 R in six minutes).

In an ORNL Review article on the Russells in 1980, Bill said, "The discovery that radiation delivered at low dose rates produces fewer mutations in mice than does the same total dose delivered at a high dose rate suggested the existence of a repair mechanism previously unsuspected."

Like other geneticists, Bill looked for a threshold dose—an exposure level below which no genetic damage is detected. In 1965 he found a possible threshold in female, but not male, mice. His and subsequent research in the Biology Division uncovered evidence that female reproductive cells can resist or repair genetic damage, even in sperm. Thus male mice exposed to a chemical mutagen and mated with females with this special capability will likely have normal offspring.

The 1973 energy crisis and gasoline shortage that resulted from the Arab oil embargo generated interest in extracting and processing shale oil and building coal gasification and liquefaction plants in the United States. The Russells received funding to explore the genetic effects of chemicals related to synthetic fuel production, using tests they had developed for radiation.

They found in the 1970s that diesel fumes and other hydrocarbons were hazardous mutagens. They wrestled with questions of whether to inject or feed the mice with a liquid chemical or force them to inhale a gas to get accurate results. Another challenge was determining the dose that reaches organs after chemical breakdown.

Bill became a trailblazer in research on the mutagenic effects on mice of energy-related chemicals. His work built on that of a British scientist and her colleagues who discovered in 1942 that mustard gas can cause mutations in fruit flies.

The World Health Organization asked Bill to study the genetic effects of hycanthone, the chemical used to treat schistosomiasis, a parasitic infection afflicting people in Africa and South America. Tests of hycanthone had shown gene mutations in some lower organisms, but Bill found no mutations in his tests on mice.

Bill's most significant discovery for chemical mutagenesis research was that of ENU. He had used Lee's spot test on many chemicals, but none of them were as effective in causing mutations as radiation until he tested ethylnitrosourea, or ENU. This cancer drug once used in the Soviet Union is related to diethyl nitrosamine, a powerful mutagen in fruit flies.

"ENU turned out to be a miracle!" Lee said. "It's the most potent mutagen in the mouse."

Unlike other chemical mutagens, ENU given in high doses to mice makes many more mutations than radiation can. ENU produces point mutations, or changes in single base pairs in a gene's DNA, whereas radiation knocks out parts of a gene or a DNA segment larger than a whole gene.

ENU has become the world's most used mutagen. Many genetics labs use ENU to screen for multiple mutated genes that predispose mammals to certain diseases.

The Russells' marriage marked a turning point in their careers and produced two children. Their mammalian genetic findings were married with other research results, helping protect the health and safety of future offspring.

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Thanks Carolyn for yet another excellently researched article. The Russells certainly were trailblazers in many ways. Their research and discoveries have proven beneficial and will continue to be among the most important in biology. And they did this in Oak Ridge! Thanks Lee for sharing your career highlights in an oral history and for helping us better appreciate Bill!

Liane (Lee) and Bill Russell, a portrait of two scientists who knew the special wonder of a shared career as well as family

Liane (Lee) and Bill Russell, a young couple living a dream

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Discoveries Bill made using mice resulted in lowering radiation exposure limits

Bill Russell, first person recognized as an ORNL fellow