Cell

Mary Frances Lyon (1925–2014)

Mary Lyon was one of the most notable geneticists of the 20th century. She is renowned for her discovery of X inactivation, an early example of epigenetic gene regulation, but she also made fundamental contributions to the entire field of genetics.

Mary was born on May 15, 1925 in Norwich, in the rural east of the United Kingdom. She was the first child of Clifford James Lyon, a civil servant, and Louise Frances Lyon (nee Kirby), a former school teacher. When she was 10, Mary's family, which by then included a younger brother and sister, moved to Birmingham. There, she attended King Edward VI High School for Girls and began her scientific career, like so many of us, through an inspirational teacher who made lessons interesting: Mary Udall, whom Mary described as having "a clear analytical mind." Mary was fascinated by physics and chemistry, but the prize she received from an essay competition, four books on nature study, ultimately led to her becoming a world-class biologist.

The Second World War helped change the status of women, and Mary decided to take the unusual step of reading natural sciences at the University of Cambridge (Girton College), where women took the same coursework as men but at that time were awarded only titular degrees. She focused on zoology and became interested in experimental embryology, graduating in 1946 with her titular degree. Rather unusually, she went on to Ph.D studies with R.A. Fisher, the Balfour Chair of Genetics at Cambridge, who founded much of the field of statistics and developed analysis methods for early gene linkage studies.

R.A. Fisher was in his fifties—brilliant, eccentric, and difficult. He threw out many who joined his lab, but he led Mary directly to her lifelong study of mouse genetics. At the time, there was no systematic method of mapping mouse genes. With 20 mouse chromosomes, Fisher decided that, if he crossed all possible combinations of his 21 visible mouse mutants, he would likely detect a new linkage. Students were each given a line of mice carrying five mutations, and Mary took on line 18, which included the "pallid" mutation. Already an insightful experimentalist, Mary was unconvinced that her mouse-crossing experiments would give her enough data for a Ph.D, but she noticed that pallid mice tended to tip their heads to one side. She found that they were missing otoliths in the inner ear and went on to investigate the effects of penetrance and to work out how otolith absence correlated with postural reflexes.

Meanwhile, Mary was reading books by Conrad Waddington, known as the father of epigenetics, and became aware of the novel idea that embryonic development depends on genes—at a time when the exact nature of a gene was unknown. R.A. Fisher was not interested in developmental genetics, and Mary needed facilities for histology; so as Waddington had returned from his wartime post (scientific advisor to the Royal Air Force) to become Professor of Animal Genetics at the University of Edinburgh, Mary moved to his department and to a new supervisor, Douglas Falconer.

Waddington and Falconer were important influences on Mary; she chose to stay in mouse genetics due to the relevance to human studies. Waddington applied to the Medical Research Council (MRC)—which unlike other funders awarded equal pay for women—and gained postdoctoral funding for Mary to stay in Edinburgh with Toby Carter, working on the inherited genetic risks from exposure to ionizing radiation, an area of great concern after WWII. Several novel mutants came out of this research, but facilities were not available for the amount of mouse breeding required, so in 1955, the entire mouse group moved to the MRC Radiobiological Research Unit at Harwell, led by John Loutit. There, Mary worked for an astonishingly productive period spanning more than 50 years. In the late 1950s, much of her research centered on the novel chromosome translocations from the Edinburgh mutagenesis work, working with Carter, Tony Searle, and one of the early great cytogeneticists, Charles Ford.

Mary Frances Lyon

Mary knew about X-linked mouse mutants since her Edinburgh days, and at Harwell she focused on mottled mutants, in which females have patches of two different coat colors. She noted that males either died in embryogenesis or had a single coat color. However, one mouse grabbed her attention (ironically, a spontaneous mutant, not a radiation mutant): a mottled male. Mary bred this male and realized that, if a mutation had occurred when he was an embryo of just a few cells, he would be a mosaic of mutated and normal X chromosomes. Her analysis led to the discovery that this could also apply to his mottled daughters, who had two types of cells: one with an active gene and one without.

Mary's knowledge that female mice (unlike female humans) need only one X chromosome for normal development and have sex chromatin in their nuclei led her straight to the work of Susumo Ohno, whom she regarded as an exceptionally creative and gifted scientist, and his discovery that the sex chromatin was a condensed X chromosome. Mary had already considered the idea that only one X chromosome is active in females, but her analysis of the mottled mouse, in the light of Ohno's discovery, led her to publish her X inactivation hypothesis in *Nature* in 1961.

This concept, now often referred to as lyonization, was not greeted with universal applause. Hans Gruneberg, a distinguished geneticist who made

important contributions to understanding human disease through mouse genetics, simply did not believe the X inactivation hypothesis. Partly, it made no sense to have patches of inactivated cells (we now know that these are clones from early inactivation events), and partly he may have thought that Mary was too young and unknown to have such a fundamental insight. Gruneberg (a clever man, whose papers are worth re-reading) was 18 years older than Mary, well-known, and had been made a Fellow of the Royal Society (FRS) in 1956. He must have been a formidable opponent, but Mary stood her ground.

In the 1980s, Mary, who only ever worked with a small group, became involved with working out the human and mouse homology maps, alongside Harwell and Oxford scientists, including John Edward. This helped to lay the foundation for the Human Genome Sequencing Project 20 years or so later. Mary made major advances in understanding the inherited effects of radiation damage and seminal contributions to many areas of mouse genetics, including the t complex, embryo freezing with David Whittingham to preserve mouse stocks, and some early work with Richard Gardner in Cambridge on mouse preimplantation embryos to determine the timing of X inactivation.

Mary also edited Mouse News Letter (MNL) (1956–1970); in the postwar environment, UK and USA mouse geneticists in particular had close and long-standing friendships and helped each other greatly. MNL was an informal publication mailed between them and other groups worldwide, providing each other with information about novel mutants and linkage groups—an important "bulletin board" in the pre-Internet world.

Mary won numerous awards and was elected an FRS in 1973 and a Foreign Associate of the US National Academy of Sciences in 1979 but was never one to push herself forward and did not receive the other honors she deserved. She was Head of Genetics at Harwell from 1962 to 1986, when she was glad to relinquish the increasing administrative burden to her successor, Bruce Cattanach. Under her stewardship, the Genetics Division had become a world-class center and was eventually established as the MRC Mammalian Genetics Unit, now directed by Steve Brown. Mary continued working productively at Harwell for many years following her official retirement in 1990. In 1998, Cambridge University held a degree ceremony at which Mary was awarded a full undergraduate degree. In 2004, the Mary Lyon Centre was opened at Harwell, in a fitting tribute to her contributions. Rather poignantly, the UK Genetics Society named a new medal after Mary last year, and though she knew of the medal, she did not live to meet its first awardee, Loeske Kruuk. Mary was diagnosed with Parkinson's disease a few years ago and died peacefully on Christmas Day, 2014.

This sums up the career, but not quite the woman. Mary was small and seemingly quiet. When one of us (E.M.C.F.) interviewed for a Ph.D position in 1983, Pete Glenister, Mary's long-time research assistant, warned "not to speak in the silences"—the silences were Mary's phenomenal mind at work, considering the data. When the other of us (J.P.) started work as a lab head at Harwell in 1978, Mary herself carried out the first set of ENU mutagenesis injections, just to help out. Mary had an extraordinary mind and memory and exceptional clarity. Her mild manner concealed an indomitable fighter on research matters where she felt strongly. She was a forward thinker and would have been thrilled to carry out experiments today using the panoply of research tools now available in mice. She also loved parties, never turning down an invitation. She was held in great affection by those who knew her, and she will be missed—an intellectual colossus, just over 5 feet tall.

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