Elizabeth Dexter Hay (1927?2007) [1]

By: Gleason, Kevin

Elizabeth Dexter Hay studied the cellular processes that affect development of embryos in the US during the mid-twentieth and early twenty-first centuries. In 1974, Hay showed that the extracellular matrix, a collection of structural molecules that surround cells, influences cell behavior. Cell growth, cell migration [2], and gene expression are influenced by the interaction between cells and their extracellular matrix. Hay also discovered a phenomenon later called epithelial-mesenchymal transition, a process that occurs during normal embryo and adult development in which epithelial cells, cells that line external and internal surfaces of the body, transform into mesenchymal stem cells [3], connective tissue cells that are capable of turning into other cell types. Hay's work helped researchers explain normal developmental processes and enabled research into abnormal processes that can cause developmental defects and diseases.

Hay was born on 2 April 1927 in St. Augustine [4], Florida, to Lucille Elizabeth Hay and Isaac Hay. She spent most of her childhood in Melbourne, Florida, with her twin brother John and her younger sister Katherine. Her father was a physician and the founder of the first local hospital in Melbourne. Following the US entry into World War II, Hay's father enlisted in the army as a physician. Hay and her family relocated to Biloxi, Mississippi, where they lived for one year. They then moved to Fort Hays, an army base near Hays, Kansas. During her high school years in Kansas, Hay took an airplane mechanics course and planned to get her pilot's license at a local school. When her father was deployed to the Philippines, Hay and her family moved back to Melbourne and away from the military base.

In 1944, Hay entered Smith College, an all-female liberal arts college in Northampton, Massachusetts. During her freshman year, Hay took an anatomy course taught by biology professor Meryl Rose, whom Hay later said influenced her to study biology. Hay joined Rose's laboratory at Smith College [5], which studied limb regeneration in salamanders.

In 1948, she graduated from Smith College [5] with a bachelor's degree in biology. According to Hay, she wanted to pursue a career in research, but opted to study medicine on the advice of Rose. Hay stated that Rose believed there were more opportunities for Hay as a woman with a medical degree. In 1948 after her graduation, Hay began studying medicine at Johns Hopkins University School of Medicine in Baltimore, Maryland, where she was one of four women in her class. By the end of her first year, Hay joined a lab that allowed her to continue her research on limb regeneration throughout medical school. During her summers, Hay performed regeneration studies with Rose at the Marine Biological Laboratory in Woods Hole [6], Massachusetts.

After obtaining her medical degree in 1952, she completed a yearlong internship at Johns Hopkins and then became an instructor of anatomy at Johns Hopkins University [7] School of Medicine in 1953. As an instructor, she taught histology [8], which is the study of the microscopic anatomy of cells and tissues. To investigate the microscopic structures of cells,

Hay began using electron microscopes in her research about limb regeneration. The electron microscope [9], which passed a beam of electrons through a subject to create an image, had a much greater magnification than traditional microscopes that relied on light to produce an image. That greater magnification enabled Hay to view the structures of cells that are present during limb regeneration.

In 1956, Hay was promoted to assistant professor of anatomy at Johns Hopkins University [7] Medical School. There, she used the school's only electron microscope [9], but she found that the images produced were of worse quality than the images she saw from other universities. According to Hay, she was unsatisfied with the quality of the images that she was producing at John's Hopkins, and she frequently traveled to Rockefeller Institute [10] for Medical Research (later called Rockefeller University [11]) in New York City, New York, for advice from experts in the field. Her trips indicated that her research would be better suited in New York, and she began applying for positions at different New York universities. Unable to obtain a fellowship at Rockefeller, Hay applied for a job under Don Fawcett, chair of Cornell University [12]'s anatomy department in Ithaca, New York. Fawcett hired Hay to run his histology [8] course in 1957.

In 1960, Fawcett became the Hersey Professor of Anatomy at Harvard Medical School [13] in Boston, Massachusetts, and secured Hay a position as an assistant professor at Harvard. Using an electron microscope [14] at Harvard, Hay continued to study the microscopic cells involved in the regeneration of salamander [15] limbs. She observed that a layer of collagen formed beneath epithelial cells during limb regeneration in salamanders. Collagen is a component of the extracellular matrix and is formed underneath the cells that line skin and organ surfaces, called epithelial cells. At the time, scientists said that collagen was produced solely by fibroblasts, a component of the extracellular matrix shown to produce collagen. Hay aimed to determine how the collagen was being formed during regeneration.

In 1963, Hay began working with Jean-Paul Revel, a Cornell postdoctoral student that moved with Hay and Fawcett to Harvard. In their experiment, Hay and Revel treated the regenerating limb of the salamander [15] with a radioactive version of a chemical called proline, which is found in large amounts in collagen. Then, they let the limb develop. Throughout its development, they could see the location of the proline by photographing it with an electron microscope [9]. Researchers had shown that a significant amount of the proline collects in the collagen layer, so they reasoned that by monitoring the movement of proline into the collagen layer, they could infer which cells were creating collagen. They found that before the proline incorporated into the collagen layer, it existed in fibroblasts as well as epithelium [16].

From that observation, Hay and Revel determined that the collagen was produced by epithelial cells in addition to fibroblasts. Because scientists had hypothesized that collagen was only produced by fibroblasts, Hay and Revel's discovery met strong skepticism. During one presentation Hay gave on their research, a colleague stood up and began arguing that it was impossible for epithelium [16] to make collagen. Hay later said that the comments and the controversy that surrounded her and Revel's discovery motivated them to continue their research on the topic.

In 1965, Hay and Revel designed an experiment to determine if collagen could be produced in the absence of fibroblasts, which would provide further evidence that epithelial cells could produce collagen. They used epithelial cells from bird eyes, which enabled them to extract and study the epithelial cells *in vitro* [17], or in laboratory glassware, which was not possible

with the regenerating limbs of salamanders that had to be observed still developing within the organism. Using that method, Hay and Revel observed that the epithelial cells produced collagen in the absence of fibroblasts, confirming their initial findings.

Hay and Revel had a further result. They observed that when the epithelial cells were not placed on an extracellular matrix, they failed to produce collagen, an indication that cells interact with their extracellular matrix during development. That additional result convinced many researchers to study extracellular matrix interactions. At that time, researchers hypothesized that the extracellular matrix played a purely structural role, meaning it provided only physical support to cells throughout the body. Hay and Revel's work, however, demonstrated that the extracellular matrix also functioned in communication and signaling between cells.

Later in 1965, Hay became a full professor of anatomy at Harvard Medical School [13], the first woman to receive tenure at that school. She was also awarded the Louise Foote Pfeiffer Professorship of Embryology for her work. Throughout the 1960s, Hay continued studying extracellular matrix interactions to see how various extracellular matrix molecules affected how a cell differentiates, the process by which a cell with the ability to become many different types changes into one specific type of cell.

In 1974, with the help of Stephen Meier, a postdoctoral student at Harvard, Hay showed that the extracellular matrix affected the differentiation [18] of epithelial cells. Specifically, they found that the abilities of specific epithelial cells to produce collagen depended on the surrounding extracellular matrix. That result helped show that the extracellular matrix can provide signals necessary for developmental events, such as the changing of one cell type to another. Throughout the 1970s, Hay studied how the extracellular matrix, specifically collagen, affected development in embryos. In 1981, Hay edited the book *Cell Biology of the Extracellular Matrix*, which summarized her and other scientists' research about extracellular matrix interactions.

Beginning in the early 1980s, Hay began to study what she called epithelial-mesenchymal transformation (later called epithelial-mesenchymal transition). Epithelial-mesenchymal transition is a process in which epithelial cells assume characteristics of mesenchymal stem cells [3], which are connective tissue cells capable of turning into different cell types. In 1982, Hay and Gary Greenburg, a graduate student at Harvard, discovered the process after taking epithelial tissues from chick [19] embryos and growing them inside of collagen gels. They observed that the epithelial cells transformed into mesenchymal stem cells [3]. In 1995, Hay summarized the process in one of her highest cited articles, "An Overview of Epithelio-Mesenchymal Transformation." Later scientists built on her research to demonstrate that the process occurs throughout embryonic development and also functions in wound healing (fibrosis). In addition to the role epithelial-mesenchymal transition plays in normal development, researchers later showed that it functions in various diseases, such as in the spreading of cancer (metastasis).

Hay received many awards for her contributions to cellular and developmental biology, including the E. B. Wilson Medal from the American Society of Cellular Biology, the Centennial Award and the Henry Gray Award from the American Association of Anatomists, and the Federation of American Societies for Experimental Biology Excellence in Science Award. During her career, Hay served as president of the American Society of Cellular Biology, the Society for Developmental Biology [20], and the American Association of Anatomists.

Hay continued her research at Harvard Medical School [13] until 2005. At Harvard, Hay mentored graduate and medical students. Outside of academics, Hay walked her four cats on leashes and collected wild mushrooms. On 27 August 2007, Hay died of cancer in Wayland, Massachusetts, at the age of 80.

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Subject

Electron microscopes [28] Extracellular matrix [29] Cornea [30] Collagen [31] Radioactive substances [32] Development, Embryonic [33] Cell differentiation [34] Extremities (Anatomy)--Regeneration [35] Microscopy [36] Electron microscopy [37]

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