In Memoriam

Elizabeth Dexter Hay – 1927-2007

Elizabeth Dexter Hay, developmental biologist, educator, and beloved mentor, died August 20, 2007. She was born in St. Augustine, Florida, on April 2, 1927. She graduated from Smith College (*summa cum laude* and *Phi Beta Kappa*) and received her MD at Johns Hopkins University in 1952 – one of only four women in the class.

After interning in medicine, Hay joined the faculty of the Anatomy Department at Johns Hopkins, where she began her extraordinary scientific career using electron microscopy to study embryological processes. In 1957, she joined Don Fawcett's Anatomy Department at Cornell Medical College to be at the cutting edge of electron microscopy and in 1960 moved with him to Harvard Medical School (HMS) as an assistant professor of anatomy. Nine years later, she was awarded the Louise Foote Pfeiffer Professorship of Embryology at Harvard. She credited Fawcett with inspiring and mentoring her as a scientist. Hay became chair of the Department of Anatomy and Cellular Biology when Fawcett stepped down in l975 – the first woman chair of a basic science department at HMS. She served as chair until 1993. Hay was an AAA member throughout her long career, having joined in 1954.

Betty Hay, AAA's 1992 Henry Gray Award recipient, is pictured here with other 1992 award winners and officers at AAA's Awards Banquet in New York. Left to right: Ray Runyan (Bensley Award), William Jollie (AAA Past President), Betty Hay, Alan Peters (AAA President), Marilyn McGinnis (Basmajian Award), R.D. Blakely (Herrick Award), Howard D. Pomeranz (Dissertation Award), Kevin Vaughn (Langman Award).

Hay's greatest scientific contribution – illuminating the role of extracellular matrix in regulating cell behavior – led to the birth of a new field of scientific inquiry and numerous honors and awards. Among these were: election to the National Academy of Sciences; the Centennial Award (AAA); the E.B. Wilson Medal (American Society for Cell Biology); election to the Institute of Medicine; Excellence in Science Award (FASEB); and the Henry Gray Award (AAA). In addition to her scientific accomplishments, she provided service and leadership to several societies associated with her discipline, including the presidency of AAA (1981-1982), American Society for Cell Biology (1976-1977), and Society for Developmental Biology (1973-1974). Her dedication and passion for science, together with her love of teaching and mentoring, are part of her profound legacy.

Hay began studying cell-extracellular matrix (ECM) interactions early in her career, being influenced by Meryl Rose while attending Smith College. Rose's encouragement sent Hay to medical school, and she continued to do research in his Wood's Hole laboratory in the summers throughout her medical school years. During this time, and as an assistant professor at Cornell, she was studying amphibian limb regeneration using electron microscopy. Right from the start, her work was provocative. Using the limb regeneration model, she and medical student Don Fischman made an important discovery with broad implications: osteoclasts arise from monocytes. Hay then found that the regenerating epidermis appeared to make collagen fibrils. She presented this work at a meeting, receiving at first a lukewarm reception, and later, confrontation and challenge, because it was believed that only fibroblasts made fibrillar collagen.

This controversy motivated Hay to more carefully investigate how epithelia produced fibrillar collagen utilizing radioactive proline, an amino acid abundant in collagen. Using electron microscopy coupled with autoradiography, she was the first to identify the specific intracellular organelles involved in collagen biosynthesis. She and collaborator Jean Paul Revel also showed the first evidence that chondrocytes synthesized and secreted fibrillar collagen via the rough endoplasmic reticulum.

In an effort to find a higher organism whose epithelium produced fibrillar collagen (as well as basement membrane components), Revel and Hay carefully documented the fine structure of the

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embryonic avian cornea. Their micrographs of the early corneal epithelium producing an acellular primary stroma are superb. To further prove her hypothesis, Hay and postdoctoral fellows Jim Dodson and Stephen Meier were the first investigators to definitively demonstrate that the embryonic avian corneal epithelium synthesizes fibrillar collagen. This was accomplished by dissecting the epithelium from the corneal stroma, putting it in culture, and assaying for the production of fibrillar collagen and glycosaminoglycans (GAGs). They also demonstrated that the cultured corneal epithelium responded to a type I collagen substratum by making more fibrillar collagen and GAGs. Through these experiments, Hay realized that epithelial cell interaction with the ECM was key to the maintenance of epithelial morphology and differentiation.

Other lines of research grew from these studies. One was with David Hasty, illuminating characteristics of the corneal fibroblast using regular EM and freeze fracture. A second was with Rozalyn Orkin, demonstating widespread occurrence of actin and myosin in a multitude of embryonic tissues. Yet another was with Sue Ann Miller using SEM to look at the surface morphology of cells in blood islands. And with Scott Miller, Hay found that tumor cells able to invade foreign species had different cell surface characteristics than those that could not invade.

Betty Hay after receiving the E.B. Wilson Medal of the American Society for Cell Biology in 1988.

As immunohistochemistry became available, Hay and postdoctoral fellows Mary J.C. Hendrix and Byrne Mayer explored the complexity and elegance of the ECM. They demonstrated the specific spatiotemporal distributions of the members of the growing collagen family in numerous developmental systems. In addition, they defined the distribution of new ECM molecules, such as the glycoprotein fibronectin, showing it to be present at the interface between cells and the scaffold provided by the collagenous fibrils in the matrix.

With postdoctoral fellow Mark Nathanson, Hay also became interested in muscle and cartilage cell transdifferentiation. Graduate student Gary Greenburg was the first to investigate how the ECM could transform an epithelial cell to a mesenchymal cell in culture. In a different avenue of research, postdoctoral fellow Jim Tomasek examined how cells moved on two-dimensional and three-dimensional matrices.

Hay and Steve Sugrue went on to demonstrate that soluble collagen, fibronectin, and laminin could all stimulate the embryonic corneal epithelial cells to synthesize and assemble fibrillar collagen. They found that removing the epithelium from the basement membrane caused cellular projections with a disorganized actin cytoskeleton. Replacement of ECM molecules reorganized the cytoskeleton to a normal structure. With postdoctoral fellow Kathy Svoboda, Hay turned her attention to detailing the corneal epithelial intracellular events corresponding to the response to ECM. These seminal observations led her to hypothesize that the cells must express special proteins on their membrane that could recognize and bind to ECM molecules and, in turn, stabilize the cytoskeleton. This hypothesis fit in with the newly emerging area of cell biology exploring cell adhesion molecules and cellular behavior. The common theme in all these projects was that cell-matrix interactions affected cellular response and behavior. Collectively, these observations launched Hay into the forefront of cell biology.

The areas of epithelial-mesenchymal transformation (EMT) and cell migration were the main research themes of Hay's laboratory until she retired from HMS in 2005. With many postdoctoral fellows and trainees, she enthusiastically explored EMT in cell culture and in the developing embryo, focusing on the formation of the neural crest and secondary palate. With postdoctoral fellow Anna Zuk, Hay examined changes in gene expression during the shift in phenotype. They were the first to demonstrate that, at the start of transdifferentiation, the ECM triggers cell adhesion molecules to localize to epithelial plasma membranes that normally do not contain any adhesion molecules. This process activates a cascade of signaling events leading to the formation of mesenchyme. Later, her EMT investigations with Dazhong Sun, Kwonseop Kim, Damian La Gamba, Deepika Walpita, and Ali

Nawshad centered on the involvement of the β-catenin-LEF-1 signaling pathway in mesenchymal formation in both cancer and embryogenesis. Hay's "fixed cortex theory" of cell migration, first proposed from work on neural crest emigration with postdoctoral fellow Mike Bilozur, held that during the transformation of an epithelial cell to a mesenchymal cell, the myosin-rich endoplasm slid into newly forming front ends while the actin cortex remained fixed to surrounding ECM. She remained productive to the end of her career, having an important role in the emerging, and now well-established, field of EMT.

Hay's research also had broad translational application, ranging from congenital developmental disorders to disease pathogenesis. Her seminal finding that the palate epithelium undergoes EMT, and not programmed cell death as believed at the time, changed the paradigm about cleft palate defects. Additionally, her lab's finding that lens epithelia transform into mesenchyme-like cells within three-dimensional extracellular matrices presented a novel mechanism for the formation of cataracts. When, in the early 1980s, she suggested that differentiated epithelia retain the ability to acquire the mesenchymal phenotype, new research initiatives emerged focusing on the central role of EMT in organ fibrosis due to abnormal wound healing (renal, pulmonary, hepatic, and cardiac fibrosis), as well as on metastasis of epithelial carcinomas. For patients with these diseases, drug development has been challenged by the complexity of the mechanisms mediating EMT, which become increasingly complicated with ongoing pathogenesis. The mechanisms for EMT remain incompletely understood; however, TGF-β inhibitors and bone morphogenetic proteins (BMPs) have shown some promise in preclinical *in vivo* models of tumor genesis and fibrosis, with TGF-β inhibitors preventing EMT and BMPs attenuating fibrosis. Thus, Hay's research, especially with respect to EMT in development and disease, has had substantial translational impact.

Betty celebrates her birthday with former postdocs Sue Ann Miller and Kathy Svoboda (standing) and Mary Hendrix and Emmy Gordon (seated) at the 2001 AAA Annual Meeting.

Being a pioneer in many ways,. Hay led the field of extracellular matrix cell biology while ushering in a new generation of scientists. She was an enthusiastic mentor, involved in projects from conception through presentation of the results at national meetings and in publications. Her passion for how the ECM influenced cellular behavior was aided by her knack for asking interesting, timely, and important questions, as well as her striving for excellence. While a talented cell and developmental biologist, Hay was also the consummate morphologist, with an exquisite eye for biological stories told by cells, which she knit together from poring over electron micrographs. Nothing excited her more than sitting at the microscope and teaching others about cells, whether her audience was faculty, postdocs, students, or family. She helped ignite the vision of numerous scientists. Her passion for science was a driving force in the laboratory and in her department.

What also had a great impact on Hay's colleagues— those in her laboratory and those in her department— was her nurturing human spirit. She would drag a frightened student through a crowded room to personally introduce him or her to a "giant" of cell biology. Never would she deem the student unworthy of such an honor. (Nor would she acknowledge the student's embarrassment.) She exhibited this type of caring while being a giant herself, and her kindnesses will be cherished forever by those who experienced them. She touched people's hearts, and those who worked with her love to exchange their favorite "Betty" stories. She indeed survives in the lives and careers of all the scientists she mentored, as well as in their professional progeny. To honor her, we will all try to mentor others with the skill and love exhibited to us by Elizabeth Dexter Hay.

Marion "Emmy" Gordon, Rutgers University
Mary J.C. Hendrix, Children's Memorial Research Center at Northwestern University
Stephen P. Sugrue, University of Florida
Kathy K.H Svoboda, Baylor College of Dentistry
Anna Zuk, Genzyme Corporation