



Eveline E. Schneeberger



Eveline Elsa Schneeberger, M.D., Professor of Pathology, emerita, died in her apartment in Cambridge on October 18, 2018, at the age of 84 after a brief illness.

Eveline was an amazing woman who lived a very full and productive life and will be remembered for her intelligence, elegance, independence, as well as somebody with the courage to speak her mind.

Eveline was born October 2, 1934 in The Hague, Holland, to Werner and Elsa (Graf) Schneeberger. From grammar school through high school, the family lived, for varying periods of time, in Indonesia, Australia, South America, and Switzerland until settling in Colorado. She graduated from the University of Colorado (Phi Beta Kappa), and continued at the University of Colorado Medical School where she earned her M.D. degree in 1959. After interning in Internal Medicine at Barnes-Jewish Hospital at Washington University, she completed a residency in Anatomic Pathology at the Strong Memorial Hospital in Rochester, finishing in 1964.

Eveline was inspired by investigative pathology and took post-doctoral training at the University of Rochester with Dr. Ashton B. Morrison and the Sir William Dunn School of Pathology with Dr. Henry Harris in Oxford, England. Her studies with Dr. Morrison showed that magnesium deficiency increased susceptibility of phosphate nephropathy. With Dr. Harris, she demonstrated by ultrastructural studies that engulfment of hen erythrocytes by HeLa cells caused by Sendai virus is due to cell membrane fusion, rather than phagocytosis, as had been assumed by Harris.

Eveline came to HMS in 1966 to work with Dr. Morris Karnovsky on the permeability of the lung, using the new ultrastructural technique developed by him using horseradish peroxidase as a tracer of cell membrane and vascular permeability. Here she began her studies of the permeability of the alveolar-capillary membrane in the lung, which was to constitute her major research efforts for the remainder of her professional life. She continued this work after joining the faculty at the Harvard School of Public Health and became an Assistant Professor of Pathology in 1968. With Dr. Robert P. Geyer she published

the first cytochemical localization of catalase in the peroxisomes in epithelial cells of the fetal lung. This localization had important implications for the ability of these cells to withstand oxidative damage after birth.

In 1972 Eveline was recruited to the CHMC by Dr. Robert McCluskey, Chief of Pathology, where she established close research relations with the immunology group of Drs. Fred Rosen and Raif Geha. Their first collaboration involved looking at the ultrastructure of human B cells. They found that activated T cells caused B cells to proliferate and secrete immunoglobulins. Her work showing increased endoplasmic reticulum and ribosomes in the activated cells was crisp, precise, definitive and clear. These were all defining traits of her personality. She continued to collaborate with Drs. Geha and Rosen for many years on the study of immune deficiency and atopic dermatitis. Her astute observations raised questions that Dr. Geha is still addressing today.

In 1979 Eveline moved to Massachusetts General Hospital (MGH) where Dr. McCluskey had been appointed Pathologist-in-Chief. She was promoted to Professor of Pathology in 1988 and remained at MGH for the rest of her research career.

Research

Eveline's major research contributions dealt with physiologic and pathologic mechanisms in the kidney, lung and immune system, primarily using ultrastructural techniques. Her studies were carefully performed, critically interpreted, well documented and beautifully illustrated. Her work was funded by NIH for over 35 years, with one R01 going for 29 years and another for 20 years.

Pulmonary Permeability Studies

Eveline's lifelong career in pulmonary structure and function began during her postdoctoral fellowship in Dr. Karnovsky's laboratory, where she carried out ultrastructural enzyme tracer experiments and made the now classical observation that the tight junctions between pulmonary alveolar cells constitute the chief permeability barrier to the passage of water soluble molecules into the alveolar space. Furthermore, in another classic study, she showed that the permeability of pulmonary endothelial cells was increased by hemodynamic forces, as by increasing intravascular volume.

At MGH Eveline developed a novel model to study the effects of plasma proteins on endothelial permeability, using fluorocarbon emulsions as oxygen carriers to replace 99% of the blood in rats. With this model, she could show directly, by immunocytochemical techniques, that the interaction of albumin or gamma globulin with the luminal glycocalyx on the endothelial cell surface is sufficient to render the endothelium less permeable to other macromolecules. This provided the first direct support for the fiber-matrix model of capillary permeability as formulated by Charles Michel at the University of London. Dr. Michel greatly admired her work and wrote a laudatory letter in support of her promotion, stating she

was “one of the two outstanding morphologists working on the lung at the present time, the other being Professor Weibel”.

In subsequent freeze fracture studies Eveline showed that the tight junctions between airway and alveolar epithelial cells as well as those between endothelial cells in different segments of the pulmonary vascular bed are structurally distinct. These studies became a standard reference and provided a structural basis not only for her earlier tracer studies but also for later physiological observations in fetal sheep. This led her to an examination of the molecular composition of tight junctions and the role that membrane lipids play in regulating tight junction activity. Using inducible expression systems, she demonstrated the contribution of the tight junction proteins, occludin and claudin-1, to the barrier function of cultured epithelial cells. Utilizing siRNA technology she demonstrated the role of individual tight junction proteins in regulating tight junction activity. Interestingly, some tight junction proteins appear to serve as receptors for certain viral and bacterial pathogens and/or their toxins. Understanding the molecular composition of tight junctions is key not only to understanding the barrier function of epithelial cells, but also to devising strategies that prevent these proteins from serving as portals of entry to a variety of pathogens.

Eveline began her longtime collaboration with Dr. Robert D. Lynch in the early 1970s. Transmission electron microscopy and freeze fracture studies on cultured fibroblasts supplemented with polyunsaturated fatty acids revealed the formation of myelin-like bodies and loss of proteins in the outer mitochondrial membrane. In later studies, she explored the role of the plasma membrane lipid environment on the structure and barrier function of epithelial cell tight junctions. Using cholesterol synthesis inhibitors and a cell-impermeant agent that could directly remove or add cholesterol to the plasma membrane, she showed that such modifications had a marked effect on the formation and stability of tight junctions of epithelial cells cultured in vitro. Results from these studies support the lipid-protein hybrid model of the tight junction barrier and a role for lipid rafts in tight junction formation and stability. Her work in lipid cell biology demonstrates, strikingly, how changes in membrane lipid composition can affect cell structure and function. She had many enjoyable adventures outside the laboratory with Bob Lynch and his family. As he mentioned, “when we were able to tear her away from the lab or office for a day or a weekend (not an easy task!), she would completely relax and enjoy the company of our family and friends.”

Another continuing interest of Eveline’s was renal pathology, encouraged by her long collaborative association with Dr. McCluskey. Her careful ultrastructural studies of experimentally induced glomerular injury documented that monocytes/macrophages migrate into the mesangium, including in T cell-mediated glomerular injury to glomerular bound antigens in experiments carried out with Atul Bhan.

Eveline was among the first to examine the biology and migratory behavior of dendritic cells in the lung. These important antigen-presenting cells are intercalated between the epithelial cells of airways. She

showed that their precursors are enriched in the pulmonary vasculature, they participate in the initiation of granulomatous inflammation and they are capable of engulfing inhaled pathogens and transporting them to local lymph nodes where they initiate an immune response. She developed an in vitro chemotaxis assay, using mouse tracheal epithelial cells, with which to monitor transient tight junction formation in dendritic cells during their trans-epithelial migration. She showed that to maintain the air-blood barrier, as they sample the inhaled air for pathogens, dendritic cells form transient tight junctions by expressing tight junction proteins.

Teaching and Clinical Work

Eveline led a laboratory section of the HMS General Pathology course from 1967 to 1985 and consistently received excellent marks in the official student evaluations. She subsequently was a laboratory leader in Renal Pathophysiology for 8 years. She was actively involved in teaching of renal and autopsy pathology to pathology residents at both MGH and CHMC. She had several post-doctoral trainees who have gone on to become professors (e.g., Nadine Cerf-Bensussan, Terasita Tuazon, Raymond Sobel). Eveline's clinical work was in renal pathology, where her ultrastructural expertise was indispensable. She was the first to demonstrate the slit diaphragms in human glomeruli that bridge between podocyte foot processes and control permeability.

Local, National and International Activities

Eveline was recognized nationally and internationally as a superb investigator, especially in pulmonary structural-functional relationships. She was invited to lecture at numerous premier scientific meetings including Gordon conferences, Keystone conferences, Ciba Symposium, and Aspen Lung Conferences. She was an invited visiting professor at many leading academic institutions in the US, UK and Switzerland. Eveline served on 17 NIH grant review committees over 25 years, including Pathology A Study Section, Pulmonary Diseases Advisory Committee, Parent Committee for Specialized Center of Research on Adult Pulmonary Diseases and others. At HMS she was a member of the Joint Committee on the Status of Women at Harvard Medical School, Chair of the Harvard Medical Society, and a member of the Admissions Committee. She served on numerous Editorial Boards including *Circulation Research*, *Tissue and Cell*, *the American Journal of Physiology: Lung Cellular and Molecular Physiology*, *The American Journal of Physiology: Cell Physiology* and *the American Journal of Pathology*.

Final Comment

Eveline had an infectious enthusiasm for science, enormous energy and deep love for her work. Her loyalty to her colleagues and friends was exemplary. In addition, she had a very strong sense of family and routinely spent Christmas in Switzerland with her mother, sister and her sister's family. She was a role model of integrity and richness of intellect, which has served her and others very well. We will

be forever grateful for having known the gem of a person and scientist. We miss her.

Submitted by,

Atul K. Bhan

Raif Geha

E. Tessa Hedley-Whyte

Robert D. Lynch

Robert B. Colvin, *Chair*