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IN MEMORIAM

rpth research & practice in thrombosis & haemostasis

Harold Ross Roberts, MD: inspirational mentor, consummate physician, superb scientist (1930-2017)

Harold Ross Roberts was known throughout the world, respected in the highest halls of research, and led international organizations, but he never lost the sense of scientific wonder and the connection to people that he learned growing up in rural Four Oaks, a town of about 1000 people in central North Carolina. That ability to connect with people characterized the rest of his life and enabled him to interact with trainees, patients, and colleagues in truly special ways. He was an inspirational mentor and leader, a consummate physician, and a superb scientist. He passed away at age 87 (just a few months after his wife, Mari) in the presence of his two sons on 9 September 2017.

Roberts was the first of his family to go to college and the first to go into medicine (Figure 1). He graduated Phi Beta Kappa from the University of North Carolina at Chapel Hill in 1952 and Alpha Omega Alpha from the UNC School of Medicine in 1955. During medical school, a two-year Student Fellowship with new Chair of Pathology, Kenneth Brinkhous, MD, started him on the road to a career in the growing field of blood coagulation and began an association with Brinkhous that would last nearly half a century. After an internal medicine internship at Vanderbilt University, he spent two years at the University of Copenhagen in Denmark as a Fulbright Scholar in Experimental Pathology in the laboratory of Tage Astrup. There, he met the love of his life, Marilyn (Mari) Claassen from Iowa, who was working in the Astrup lab. Over his career, he and Mari would return to Denmark twice for sabbaticals, one at the University of Aarhus in the laboratory of Stefan Magnusson and one at Novo Nordisk with Ulla Hedner, where he discovered the β isoform of tissue factor pathway inhibitor (TFPI). The next five years saw him return to Vanderbilt for Residency, back to Chapel Hill for a Fellowship in Pathology, back to Vanderbilt for a Fellowship in Hematology, and back to Chapel Hill for a Fellowship in Neurology and further research training in Pathology. In 1964, he joined the faculty at UNC as Assistant Professor of Pathology and Medicine, was promoted to Associate Professor in 1967, and in 1968, at the age of 38, became Chief of the Division of Hematology-Oncology. He was promoted to Professor in 1970 and named Sarah Graham Kenan Professor, the highest regarded professorship at UNC, of Medicine and Pathology, in 1986. From 1977-1980, he was the founding Director of the Comprehensive Hemophilia Diagnostic and Treatment Center, which now bears his name and which was one of the pioneering Centers for Comprehensive Care of any disease (Figure 2). From 1978 to 1998, he was founding Director of the Center for Thrombosis and Hemostasis at UNC. Over the span of his career, he would publish 345 articles and edit 12 books. He was continuously funded by the NIH for 42 years, was principal investigator for 15 years of a Program Project Grant from the National Heart Lung and Blood Institute (NHLBI), and was one of four scientists in the US, along with Ralph Nachman at Cornell, Robert Colman at Temple and Philip Majerus at Washington University, to receive funding for the prestigious Specialized Centers of Research (SCOR) in Thrombosis. He was Chair of the Hematology Study Section at NIH an unprecedented three times and those that served with him will remember the efficiency with which he ran those meetings. He also chaired the Program Project Grant Review Committee, served on and chaired the Advisory Board of the Division of Blood Diseases and Resources (DBDR), and served on the Advisory Board and Board of External Advisors of the NHLBI. His insight and comprehensive knowledge of the world of thrombosis and hemostasis was greatly valued by NHLBI. That same insight and knowledge led him to chair the Medical and Scientific Advisory Board of the National Hemophilia Foundation, chair the Hemostasis Gordon Research Conference, and serve a term as Councilor for the American Society of Hematology.

For more than 40 years, Roberts was a driving force in the International Society on Thrombosis and Haemostasis (ISTH). He joined the organization in 1966, when it was known as the International Committee on Thrombosis and Hemostasis (ICTH). He played a significant role in the founding of the ISTH in 1969, becoming a charter member, and the transition of the ICTH to the Scientific and Standardization Committee (SSC). He was elected to the SSC in 1972 and chaired the Task Force on Factor IX Standards. In 1976, he became Secretary-General of the ISTH, succeeding Brinkhous, and in 1987 that position transitioned to Executive Director, a position he held until 1999. From 1999 until 2007, he was Senior Associate Editor to Editor Pier Mannucci for *Thrombosis and Haemostasis*, and together they very successfully started a new journal owned by ISTH - the *Journal of Thrombosis and Haemostasis*, which debuted in 2003 and opened with a remarkable impact factor of 4.8. He received the Distinguished Career Award for Contributions to Hemostasis and, in 1995, the Robert P. Grant Medal, the ISTH's highest honor. In 2005, in recognition of his important and longstanding contributions to the ISTH, the Harold R. Roberts Medal was established to celebrate the contributions of individuals to the SSC (Figure 3).

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FIGURE 1 Harold Ross Roberts, MD

FIGURE 2 Roberts and colleagues at the UNC Comprehensive Hemophilia Diagnostic and Treatment Center and officials from the Chiron Corporation infusing the first *in vivo* gene therapy on September 14, 1999 in the General Clinical Research Unit at the University of North Carolina. From left to right, Aime Grimsley, RN, Gil White, recipient, Roberts, Brenda Nielsen, RN, unidentified Chiron Corporation employee, Paul Monahan, MD, Deborah Hurst of Chiron Corporation, and Chris Walsh, MD

FIGURE 3 The Harold R. Roberts Medal. Established in 2005, the Harold R Roberts Medal recognizes individuals who have used their time and talents to support the mission of the ISTH's Scientific and Standardization Committee (SSC). https://www.isth.org/?page=Awards

Scientifically, Roberts made many seminal contributions to our field, but two stand out. The first was a body of work on hemophilia B, starting with the demonstration that many patients with hemophilia B contained antigen that reacted with a factor IX antibody (cross reacting material or CRM was a term he coined) and going through the cloning of factor IX and characterization of molecular defects in patients. The molecular characterization of factors IX Chapel Hill, Alabama, Hilo, and New London were from his laboratory. This work was on the leading edge of the molecular biology revolution that hit the blood coagulation field in the 1970s and 1980s. The second contribution was the development of an *in vitro* cell-based model which Roberts, Monroe, and Hoffman used to integrate all elements of blood coagulation. Together with Hedner, Ezban and Kjalke at Novo Nordisk, they used this model to evaluate the mechanism of action of factor VIIa in hemophilia and to make other advances in our understanding of coagulation and the way bypassing agents affected the generation of thrombin - really the burst of thrombin generation - that was hemostatically important. From a larger perspective, this was part of a collection of work that led to the concept of thrombin generation and the development of thrombin generation assays that are increasingly seen as predictive of hemostatic response.

During his career, he received numerous honors, including the French International Prize for Research in Hemophilia, the Kenneth Brinkhous Award from the US National Hemophilia Foundation, the Karl Landsteiner Award from the American Association of Blood Banks, the Medical Alumni Distinguished Faculty Award from UNC, and the Henry Stratton Medal and the Mentor Award from the American Society of Hematology. He received an honorary degree from the University of Lund and was named a Caballero of the Orden Heráldica de Cristóbal Colón of the Dominican Republic. His own institution also recognized him. The Hemophilia Center at UNC is named the Harold R. Roberts Comprehensive Hemophilia Diagnostic and Treatment Center in his honor, a medical school Scholarship is named for him, and there is an endowed Harold R. Roberts Chair in the Department of Medicine at UNC.

We, the authors, came to know Professor Roberts as medical students and hematology trainees. For students, he was *the* teacher, able to bring basic biology and clinical principles together in a way that was exciting and memorable, that led to a true understanding of pathophysiology, and that naturally led to scientific inquiry. For more than a decade, the number of students choosing hematology as a career was notably increased because of his teaching ability. Upon creation of the Harold R. Roberts Distinguished Professorship in the Department of Medicine at UNC in November 2000, one of us (G. C. White) was asked to make a few remarks about Roberts. In preparation for those remarks, I wondered why Roberts had this effect on people like me. Clearly, he was a gifted teacher who was able to convey complex concepts in understandable ways and in ways that engendered excitement. He had outstanding, encyclopedic command of his field, and a logical, common sense way of seeing what was important and what was not. Those who sat on study sections with him can testify to that. He was devoted to hematology, to research, and to the notion of the physician-researcher. And he was uncommonly loyal to friends. But I concluded that what he did best was knowing how to make you believe in yourself and this is the essence of mentoring – teaching a person how to do what needs to be done and then helping them to believe in themselves.

Despite all the personal accolades and accomplishments over a rich career, Roberts' lasting legacy is people. It is impossible to list all the individuals that came under his influence, but it includes Agre, Blatt, Briet, Broze, Carr, Cederbaum, Church, Cines, Costa e Silva, Escobar, Eckler, Francis, Gabriel, Goldsmith, Gonzalez, Gray, Hassall, High, Hoots, Hiskey, Kempton, Kingdon, Knupp, Larson, Lechler, Liles, Lozier, Lundblad, Macik, Marbet, Moll, Monroe, Negier, Nichols, Parker, Rackoff, Saba, Sallah, Snipes, Sorrentino, Stafford, Tabares, Taylor, Tokaz, Walsh, Weiss, White, Wolberg, Wong, and Zeitler. There are 21 hemophilia treatment centers in 8 countries that are or have at one time been led by Roberts' trainees; his trainees have been leaders of Schools of Medicine, industry, US NIH, and regulatory agencies; they have won Nobel prizes, ASH awards, AHA awards, and ISTH awards. He went forth and multiplied.

In summary, Roberts was a charter member of ISTH and the Secretary General/Executive Director of ISTH from 1976 to 1999. He led the organization with grace and skill and, along with many others, guided the steady growth of the organization and its influence in the field. He did this while maintaining an active academic career as a basic and clinical researcher, beloved teacher, and insightful physician and he influenced the lives of a generation of scientists in the field of thrombosis and hemostasis who continue in his footsteps. Most especially, however, Roberts never forgot his humble roots and always engaged colleagues, patients, trainees, and students - no matter their circumstance - with respect, dignity, compassion, and humanity.

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