# OBITUARY OF NORMAN K. HOLLENBERG

(1936-2020)


## MURRAY EPSTEIN

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*Norman K Hollenberg*

Norman K. Hollenberg, M.D., Ph.D., renowned leader in cardiovascular medicine and hypertension, passed away on January 15th, 2020, after a long illness. Dr. Hollenberg was Professor of Medicine and Radiology and Director Director of the Physiologic Research Division in the Department of Radiology at the Brigham and Women's Hospital and Harvard Medical School. He leaves a remarkable lasting legacy in nephrology, hypertension and in medicine broadly.

Dr. Hollenberg was born in Winnipeg, Manitoba, and was a member of one of the most illustrious medical families in Canada. He earned his undergraduate and medical degrees at the University of Manitoba. His Ph.D. in Pharmacology was obtained under Professor Börje Uvnäs at the Karolinska Institute in Stockholm, Sweden and Professor Mark Nickerson at the University of Manitoba and McGill University in Canada.

After a medical residency in Winnipeg Norm completed his nephrology fellowship in the Cardiorenal Unit of the Peter Bent Brigham Hospital in Boston, under the tutelage of John Merrill, M.D., considered by many to be the renowned founder of modern nephrology as we know it today. Although Uvnäs, Nickerson and Merrill all had an enormous influence on Norm's approach to biology and medicine, his value system, and his dedication to academic pursuits, I believe that Mark Nickerson and the academic environment at the University of Manitoba had the most profound impact in nurturing Norm's scientific discipline and thirst for knowledge.

I first met Norm when I arrived at the Peter Bent Brigham in July of 1966 to start my nephrology fellowship. Our Chief, John Merrill, tasked Norm to "bring me up to speed". I collaborated with Norm in his early studies of intrarenal hemodynamics in both healthy individuals and those with a wide array of diseases[1,2,3]. Our initial studies utilizing the companion modalities of selective renal arteriography and 133 xenon washout curves succeeded in demonstrating that a redistribution of intrarenal perfusion with resultant cortical ischemia mediated acute renal failure[1]. We subsequently succeeded in extending this investigative approach to studies of patients with Hepatorenal Syndrome and demonstrated a preferential reduction in renal cortical perfusion[3]. Subsequently we succeeded in conducting postmortem angiography in the kidneys of 5 patients studied during life. Our findings disclosed a striking normalization of the vascular abnormalities. In concert these studies provided compelling evidence for the functional basis of the renal failure of patients with decompensated cirrhosis.

Norm and I became not only research collaborators, but virtual brothers, frequently traveling worldwide to attend medical congresses, and sharing life cycle events.

From its beginning, Dr. Hollenberg's career focused on the kidney. Over an academic career exceeding 50 years, his extensive and groundbreaking research solidified his position as one of the true giants in the regulation of the renal circulation in both health and disease. Norm's research productivity was enormous

and he authored more than 600 publications. His many accomplishments included documenting the factors (both hormonal and environmental) that control the renal circulation, and delineation of the mechanisms whereby these mediators modulate renal function to subserve both volume and sodium homeostasis. Concomitantly he assessed how dysfunction and dysregulation of these modulators promote the development of a wide array of disease states including hypertension, diabetic nephropathy and congestive heart failure [4]. Much of his research was the product of decades-long collaboration with his close friend, Dr. Gordon Williams, who is Professor of Medicine at Harvard Medical School as well as the Director of the Hormonal Mechanisms of Cardiovascular Injury Laboratory at Harvard's Brigham and Women's Hospital.

Dr. Hollenberg's contributions to the current paradigms for the management and treatment of hypertension were profound. He was a pioneer in the development of new therapeutic agents that modulated the renin-angiotensin system, and their application in the treatment of a wide array of diseases in order to attenuate, abrogate and even reverse many cardiovascular and renal disorders. He was the first investigator to administer an ACE inhibitor to a patient with congestive heart failure, at a time when the prevailing wisdom asserted that this new drug would be fatal. Norm proved the "nay sayers" wrong. The patient was able to ambulate and ultimately be discharged to return home.

Dr. Hollenberg' s groundbreaking research was complemented by concurrent studies by his life-long friend, Professor Mattias Aurell of the Sahlgrenska Hospital and the University of Gothenburg, Sweden who was the first investigator to demonstrate that infusions of subpressor doses of angiotensin II markedly increased sodium reabsorption in the renal tubules in humans.

Dr. Hollenberg's contributions to the world of hypertension were profound. As a consequence of his insights and formidable clinical investigations, Dr. Hollenberg's research catalyzed the development of two important classes of drugs, ACE inhibitors and angiotensin receptor blockers, which constitute the mainstay of our current treatment of hypertension. Today these two major classes of medications are prescribed to millions of patients for the treatment of hypertension, for afterload reduction in the treatment of congestive heart failure and for abrogating and attenuating progression of chronic kidney disease, particularly in patients with diabetes mellitus.

An additional research interest of Dr. Hollenberg, which has mesmerized me and many members of the International society of Hypertension, focused on the vascular effects of flavonoid-rich cocoa. Of note, cocoa is the richest known source of flavanols. Norm's studies married medical anthropology and the important arena of vascular responsiveness [5]. A true medical detective – Dr. Hollenberg was intrigued by initial reports of low to normal blood pressures of the Kuna Amerinds of the San Blas islands of Panama. Norm posed an obvious question; was the absence of hypertension attributable to protective genes or environmental factors. Consequently, Hollenberg and colleagues initiated a series of comprehensive studies of the Kuna Amerinds that provided the link to our understanding of this clinical observation, increased oxidative stress and impaired nitric oxide bioavailability to be the principal features of vascular dysfunction, detectable as abnormal coronary vasomotion[5]. Based on Dr. Hollenberg's seminal research, a large clinical trial is currently underway to determine whether flavanols found in chocolate may confer health benefits, including lowering blood pressure and the risk for cardiovascular disease, the COSMOS study - (The COcoa Supplement and Multivitamin Outcomes Study).

Beyond research, Dr. Hollenberg had a special interest in medical education and teaching. Norm's door was always open in welcome. Over the decades, he mentored countless students and fellows, many of whom became professors and leaders in their communities around the world. He served as one of four Associate Editors at the New England Journal of Medicine for seventeen years. He also served on the editorial boards of a dozen journals, as the Editor of the Atlas of Hypertension and importantly for the members of ISH, the longtime Editor-In-Chief of Current Hypertension Reports.

The world of medicine, especially the Hypertension and Nephrology communities, have lost one of its giants. Norman Hollenberg was truly one of the great leaders in hypertension and renal medicine. The world has lost a kind and caring human being.

His wisdom and deep warmth are legacies that will be treasured by the members of the international Society of Hypertension, and medicine at large. On a personal level, Norm served informally as my longtime consigliore and confidant and we enjoyed a warm and extended friendship, sharing many life cycle events.

Norman Hollenberg is survived by his daughter Ilana Hollenberg, his son David Hollenberg, and his beloved and loving wife of 35 years, Deborah, who stayed close by his side, caring for him with all her love and strength until he left us.

**Murray Epstein - murraye@gate.net**

*Photograph by Christer Andersson, Umeå, Sweden*

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