J Am Soc Nephrol 13: S1–S2, 2002

The Career of Lee W. Henderson

JONAS BERGSTROM,[‡1] MICHAEL LYSAGHT,* and ALFRED K. CHEUNG[†]
[*]Brown University, Providence, Rhode Island; [†]University of Utah, Salt Lake City, Utah; and [‡]Karolinska Institute, Huddinge, Sweden.

The remarkable career of Lee West Henderson spanned the entire era of maintenance dialysis. Henderson began his dialysis career by serving as a Research Associate and Chief Fellow in John Merrill's laboratory at Brigham and Women's Hospital in 1961. At that time, dialysis was largely limited to the treatment of acute renal failure. During the ensuing 40 yr, dialysis has become routine treatment for chronic renal failure and is now serving over one million patients worldwide. During this period of time, Henderson made a number of seminal contributions to the development of extracorporeal treatments for uremia while holding important posts at the University of Pennsylvania and the University of California at San Diego, as president of the American Society of Artificial Organs, as a founder of the International Society of Blood Purification, and as the second Editor-in-Chief of the *Journal of Blood Purification.* In 1988, he moved to the Baxter Healthcare Corporation as the Vice President for Scientific Affairs in the Renal Division. There, he supported the field of nephrology in a different, but no less influential, capacity. Notwithstanding all his other career achievements, Henderson will most likely be remembered and judged on the depth, breadth, and impact of his peer review publications.

Peritoneal Transport

One of his landmark publications related to peritoneal dialysis and was jointly published in the *Journal of Clinical Investigation* in 1969 in collaboration with K. Nolph (1). The paper is particularly noteworthy for two reasons. (*1*) It contained, in the appendix, a kinetic model for mass transport of urea from the blood to the peritoneum. To our knowledge, this represented the first such published model. Despite the many simplifications (for example, constant peritoneal volume and purely diffusive transport), the equations in that model yielded results that were very similar to the more elaborate models constructed by later workers (2). (*2*) In the same publication, Henderson and Nolph identified the similarity in sieving coefficient between urea (molecular weight, 60 Da) and inulin (molecular weight, 5200 Da) and noted that this was paradoxical. The permeability profile of the peritoneal membrane constructed from these results was similar to that of the glomerulus and was very different from the conventional (low-flux) cellulosic hemodialysis membranes that were used in that era. This finding, along with the middle molecule hypothesis put forth by Scribner (3), stimulated an intense search for synthetic membranes with transport properties similar to the glomerular filtration barrier for use in extracorporeal circulation.

High-Permeability Membranes

The search for high-permeability membranes achieved its first major success in the late 1960s, when Henderson worked with L. Bluemle on a project sponsored by the National Institutes of Health (NIH) to evaluate hemodialyzers. During the course of the project, Henderson became aware of the polysulfone membrane developed by the Amicon Corporation. The Amicon membranes were highly permeable, yielding high filtration rates at low transmembrane pressures. Furthermore, they could be fabricated to provide good size selectivity, with a molecular cutoff of ~50,000 Da. The availability of these membranes with resemblance to the glomerular filtration membrane allows for the testing of the middle molecule hypothesis. Consequently, Henderson wrote his contract officer at the NIH to change the objectives of the contract and refocus his research career on the development of hemofiltration that use high-permeability synthetic membranes.

It took innovation, perseverance, and years of hard work, but the concept of hemofiltration finally reached clinical practice. The high-flux membranes were spun into the hollow-fiber format and became the first "biocompatible" membranes to reach the clinic. Henderson and colleagues (4) were the first to identify that polysulfone membranes (made by Amicon) affected leukocyte function less than conventional cellulosic membranes. Subsequently, many publications have shown that polysulfone membranes activate the plasma complement system and neutrophils less than unmodified cellulosic membranes.

Another major byproduct of the hemofiltration project was the development of isolated ultrafiltration for the treatment of fluid overload (5). The application of this concept to the treatment of acute renal failure by P. Kramer *et al.* (6) formed the basis of continuous arteriovenous hemofiltration, which became the predecessor of various continuous renal replacement therapies used nowadays.

Hemofiltration

The principal focus of these high-permeability synthetic membranes by Henderson and his colleagues during the late

[1] Deceased.

Correspondence to Dr. Alfred K. Cheung, Dialysis Program, 85 North Medical Drive East, Room 201, University of Utah, Salt Lake City, UT 84112. Phone: 801-581-6427; Fax: 801-581-4750; E-mail: alfred.cheung@hsc.utah.edu

1046-6673/1300-0001
Journal of the American Society of Nephrology

1960s to the mid-1970s was intermittent hemofiltration, which was known as hemodiafiltration at the time. The *in vitro* and *in vivo* performance of this convective blood cleansing modality was rigorously described in two seminal papers in 1975 (7,8). Because of the large quantity of fluid that needed to be exchanged during hemofiltration, a volumetric fluid cycler was developed in which paired reciprocal pumps provided fluid balance. Variants on such systems have replaced the cruder equipment originally used for conventional dialysis. As the volumes of fluids being infused further increased, Henderson developed an in-line ultrafilter and demonstrated that a single pass through a fresh anisotropic, hydrophobic membrane with the appropriate molecular cutoff rendered ordinary dialysate sterile, pyrogen-free, and suitable for intravenous infusion during hemofiltration (9). The mechanisms of removal of the contaminating particles were further identified as a combination of filtration and adsorption. The concept of adsorption onto artificial membranes as a mean of solute removal has since been widely examined in various hemodialysis or hemofiltration circuits. In addition, this technique of fluid purification has been applied to generate on-line, sterile, pyrogen-free dialysate and hemofiltration substitution fluid in commercial delivery systems.

Interleukin Hypothesis

The interleukin hypothesis was published in 1983 by Henderson *et al.* in the introductory issue of the *Blood Purification* (10). At the time, complement activation and neutropenia were the two primary indices of bioincompatibility evaluated by the hemodialysis researchers. The novel interleukin hypothesis not only described the intradialytic activation of another important blood component—namely, the circulating monocyte—it also proposed the association of a laboratory biocompatibility index with clinical abnormalities. This hypothesis set the paradigm for dialysis membrane biocompatibility research for the next decade.

It is indeed impressive that so many of the key enabling technologies for contemporary hemodialysis had their origins from hemofiltration, which was perhaps Henderson's most significant innovation and contribution to medicine and bioengineering. These spin-offs include synthetic high-flux membranes, cytokine production during extracorporeal circulation, volumetric fluid cyclers, middle molecule removal, convective solute transport, and pyrogen exclusion filters.

Research Funding

Henderson's personal and collaborative research accomplishments alone would be ample for most investigators; however, he managed a superlative encore in the form of the Extramural Grant Program (EGP) after he took on the research administrative responsibility in Baxter Corporation. To put this program in context, we need to return to the late 1980s and early 1990s, when funding from the NIH, especially for chronic renal failure and dialysis research, was restricted. That was a difficult era for the NIH, after nearly a decade of government down-sizing and before the legislature decided that medical research was a high priority for federal spending. The NIH was trying to maintain existing programs, but there were insufficient funds to support new initiatives or young investigators. Into this breach came the EGP, which for nearly a decade, and long after the NIH drought eased, provided research dollars to worthwhile investigative initiatives in Nephrology. Research proposals for the EGP were reviewed by an independent board of reputable nephrologists and biomedical engineers. The review process of the EGP was impartial and noncommercial. The criterion for funding was scientific excellence. The result of the program was impressive. Through one decade after its initiation, the EGP dispersed $25 million for >700 projects in 22 countries, resulting in >700 publications, with an average impact factor of 4.9. The success of the program hinged substantially on Henderson's insight, creativity, leadership, and knowledge of the field, personnel, and academic environment.

We live in a time punctuated by the retirement of most pioneers in chronic dialysis. They are a unique and important collection of individuals. It is indeed a pleasure to dedicate this issue to one of the most admired and respected of the group.

References

1. Henderson LW, Nolph KD: Altered permeability of the peritoneal membrane after using hypertonic peritoneal dialysis fluid. *J Clin Invest* 48: 992-1001, 1969
2. Waniewski J, Werynski A, Heimburger O, Lindholm B: A comparative analysis of mass transport models in peritoneal dialysis. *Trans Am Soc Artif Intern Organs* 37: 65–75, 1991
3. Scribner BH: Discussion. *Trans Am Soc Artif Int Organs* 11: 29, 1965
4. Henderson LW, Miller ME, Hamilton RW, Norman ME: Dialysis leukopenia, polymorph random mobility and the control of peripheral white blood cell levels: A preliminary observation. *J Lab Clin Med* 85: 191–197, 1975
5. Silverstein ME, Ford CA, Lysaght MJ, Henderson LW: Treatment of severe fluid overload by ultrafiltration. *N Engl J Med* 291: 747–751, 1974
6. Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F: Arteriovenous haemofiltration: A new and simple method for treatment of over-hydrated patients resistant to diuretics. *Klin Wochenschr* 55: 1121–1122, 1977
7. Colton CK, Henderson LW, Ford CA, Lysaght MJ: Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow fiber blood ultrafilter. *J Lab Clin Med* 85: 355–371, 1975
8. Henderson LW, Colton CK, Ford CA: Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. *J Lab Clin Med* 85: 372–391, 1975
9. Henderson LW, Beans E: Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. *Kidney Int* 14: 522–525, 1978
10. Henderson LW, Koch KM, Dinarello CA, Shaldon S: Hemodialysis hypotension: The interleukin hypothesis. *Blood Purif* 1: 3–8, 1983