

This Week's Citation Classic

Babb A L, Popovich R P, Christopher T G & Scribner B H. The genesis of the square meter-hour hypothesis. *Trans. Amer. Soc. Artif. Internal Organs* 17:81-91, 1971. [Depts. Nuclear Engineering, Chemical Engineering, and Medicine, Univ. Washington, Seattle, WA]

In 1965, we believed that there may be uremic toxins that behaved as though they had molecular weights larger than urea (60 daltons). Based on a retrospective study of our first patients on dialysis, together with a new kinetic model of toxin transport and in vitro and in vivo experiments, we deduced that their apparent molecular weight was in the 2,000-5,000 dalton range. These insights led to the 'Square Meter-Hour Hypothesis.' [The *SCI*[®] indicates that this paper has been cited in over 245 publications since 1971, making it one of the three most-cited papers ever published in this journal.]

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"In 1961, B.H. Scribner, a nephrologist, invented the arteriovenous shunt for providing continuous access to the cardiovascular system of patients with end stage renal disease. At that time, a crude and costly refrigerated 400 liter stainless steel tank was used to contain the aqueous solution of chemicals recirculated through a hemodialyzer, which consisted of three parallel double layers of a cellophane membrane between which blood flowed by the pumping action of the heart. The aqueous solution, or dialysate, was pumped on the outside of the membranes and the uremic toxins passed from the blood to the dialysate through the membrane by the process of dialysis. The cleansed blood was then returned to the patient.

"The patients were treated for 12 hours twice weekly. There were so many candidates for treatment and so little money to provide therapy to all, that the so-called 'Who Shall Live?' committee was formed by the local medical society to select patients for treatment. Having been turned down for federal funds, in desperation Scribner called the chairman of the department of chemical engineering, R.W. Moulton, for some engineering assistance. Moulton recommended me.

"I met with Scribner and his colleagues shortly thereafter and was soon caught up in developing the lower cost continuous systems summarized in a recent review.¹ In a subsequent meeting, Scribner made the observation that 'in contrast to our early experience with hemodialysis, neuropathy was not seen in our first chronic peritoneal dialysis patients

even though their urea nitrogen and serum creatinine levels were considerably higher than those of most hemodialysis patients who developed this complication.' He postulated that since the peritoneum leaked protein during peritoneal dialysis, it might also be passing toxins of higher molecular weight than urea relatively more efficiently than the cellophane membranes in hemodialyzers. My group then developed mathematical models, and designed protocols for *in vitro* and *in vivo* confirmation. One of the group, R.P. Popovich, stayed on for postdoctoral work and ultimately became a co-inventor of the Continuous Ambulatory Peritoneal Dialysis (CAPD) scheme² while at the University of Texas. Another member, T.C. Christopher, is now in private practice as a nephrologist.

"The initial results of our efforts resulted in the 'Square Meter-Hour Hypothesis' in which it was assumed that in uremia there were large molecular weight toxic solutes in the 2,000-5,000 dalton molecular weight range. For these solutes, it was also assumed that doubling the hemodialyzer surface area would cut the time in half for the equivalent so-called 'middle molecule' removal.

"This publication attracted worldwide attention because it was the first attempt to quantify the kinetics of the removal of potential uremic toxins of higher molecular weight and led to the concept that large surface area dialyzers could dramatically reduce treatment time. There is now a plethora of large surface area hemodialyzers on the market. Subsequent research led us to believe that the middle molecules were in the 500-2,000 dalton range and to enunciate the 'Middle Molecule Hypothesis.'³ These two hypotheses triggered a worldwide search for evidence of middle molecules in uremic plasma.⁴

"Although we were unaware of early experimental work that suggested the existence of middle molecules in uremia, a group in Sweden successfully fractionated uremic plasma in 1976 and found that certain middle molecule fractions exhibited toxicity *in vitro*.⁴ No definitive studies of *in vivo* toxicity of middle molecule compounds have yet been carried out.

"I believe that the publication cited here together with concomitant contributions to dialysis theory and technology were the major reasons for my election to the US National Academy of Engineering in 1972 and the Institute of Medicine of the National Academy of Sciences in 1982."

1. **Babb A L & Scribner B H.** Dynamics of hemodialysis systems. (Cooney D O, ed.) *Advances in biomedical engineering, Part I.* New York: Marcel Dekker, 1980. p. 93-141.
2. **Popovich R P, Moncrief J W & Decherd J B.** Continuous ambulatory peritoneal dialysis. *Ann. Intern. Med.* 88:449-56, 1978.
3. **Babb A L, Farrell P D, Uvelli D A & Scribner B H.** Hemodialyzer evaluation by examination of molecular spectra: implications for the square meter-hour hypothesis *Trans. Amer. Soc. Artif. Internal Organs* 18:98-105, 1972.
4. **Bergström J, Fürst P, Asaba M & Oules R.** Dialysis and middle molecules *Dialysis Transplant* 7:344-7, 1978.