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This Week's Citation Classic

Weiner I M & Mudge G **H.** Renal tubular mechanisms for excretion of organic acids and bases. *Amer. J. Med.* 36:743-62, 1964. [Dept. Pharmacology and Exp. Therapeutics, Johns Hopkins Univ., Sch. Med., Baltimore, MD and Dept. Pharmacology and Toxicology, Dartmouth Med. Sch., Hanover, NH]

The review covered renal excretory patterns of various organic electrolytes including uric acid. Special emphasis was placed on the recently discovered phenomenon of bidirectional transport of drugs: active tubular secretion and passive reabsorption by nonionic diffusion. [The ***SCI***® indicates that this paper has been cited over 215 times since 1964.]

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"This paper was one of a series of short reviews in a symposium issue of the *American Journal of Medicine*. The guest editor, R.W. Berliner, had invited G.H. Mudge to prepare the review and the latter asked me to collaborate. Until two years earlier I had been one of Mudge's junior colleagues. To a considerable extent the review was based on material which followed from our 1959 paper.[1] The paper had been published in an institutional journal, the very vehicle used by E.K. Marshall, Jr., for his initial proof *of* tubular secretion in the mammalian kidney.[2] Mudge, who is about to retire from laboratory work, was and still is as fond *of* historical connections as he is *of* experiments yielding unexpected results.

"Our contributions in this area stemmed from a fortuitous event. We had been trying to understand why acidification *of* the urine enhanced and alkalinization diminished the renal response to organic mercurials, a class of diuretics which is now virtually obsolete. It was of interest to learn the sites of acidification within the nephron. Our plan was to do stop-flow experiments in animals treated with salicylate. Stop-flow experiments allow crude localizations of nephron functions and salicylate was thought to distribute across the tubular epithelium by nonionic diffusion, i.e., it was to serve as the pH indicator for the fluid in various nephron segments. Our initial results with salicylate made no sense in this context and further work demonstrated that salicylate is subjected to active tubular secretion as well as reabsorption by nonionic diffusion. This complex excretory pattern had been entertained as a possibility for antimalarial drugs years earlier by Jailer, Rosenfeld, and Shannon[3] but the idea seems to have been treated with total, perhaps benign, neglect. We, and others, were unaware of the suggestion at the time of our initial work. As indicated in our review and by much subsequent work, this excretory pattern for organic electrolytes is quite common, but not universal. Recent reviews of this subject are cited in the article by Barbara Rennick.[4]

"It is difficult to pinpoint the reason or reasons why a review is cited frequently. Several ideas come to mind. First, most of the more recent reviews of this subject have appeared in books. Books may be too expensive for many individuals or libraries. Second, an area of research may not progress rapidly and an older review may retain its usefulness. Third, a review sometimes contains the most explicit exposition *of* an idea. Finally, editors of reviews tend to be more generous than editors of scientific reports; this factor makes it easier for authors of reviews to cover interrelationships, some speculative, that might be excluded from a regular paper."

1. **Weiner I M, Washington J A, II & Madge** G **H.** Studies on the renal excretion of salicylate in the dog. *Bull. Johns Hopkins Hosp.* 105:284-97, 1959.
2. **Marshall** E **K, Jr.** & **Vickers J** L. The mechanism of the elimination of phenotsulphonephthalein by the kidney—a proof of secretion by the convoluted tubules. *Bull. Johns Hopkins Hosp.* 34:1-7, 1923.
3. **Jailer J W, Rosenfeld M & Shannon J A.** The influence of orally administered alkali and acid on the renalexcretion of quinacrine, chloroquine and santoquine. J. *Clin. Invest.* 26:1168-72, 1947.
4. **Rennick B R.** Renal tubular transport of organic cations. *Amer. J. Physiol.* 240:F83-9, 1981.