CC/NUMBER 7
FEBRUARY 16, 1981

This Week's Citation Classic

Milne M D, Scribner B H & Crawford M A. Non-ionic diffusion and the excretion of weak acids and bases. *Amer. J. Med.* **24**:709-29, 1958. [Dept. Medicine, Postgraduate Medical Sch. London, England]

Biological membranes are more permeable to the unionized fraction of lipid soluble weak bases and acids than to the ionized component. This accounts for more rapid excretion of many organic acids in alkaline urine and of weak bases in acid urine. Mathematical analysis allowing for a) slight permeability to the ionized component, b) slowness of full equilibration across the membrane, and c) limited capacity of available renal blood flow, gives a reasonable correspondence between observed and theoretical clearances of many such acids and bases. [The *SCI*® indicates that this paper has been cited over 315 times since 1961.]

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January 14, 1981

"My colleagues, B.H. Scribner and M.A. Crawford, and myself are flattered to have our paper and names included in the most-cited item list. This paper was an invited script in a group of papers devoted to advances in renal physiology, and stemmed from my visit to the US in 1957. My own interest in this field was stimulated by work reported from R.A. McCance's laboratories in Cambridge, England, where it was shown by use of the carbonic anhydrase inhibitor, acetazolamide, that increased excretion of ammonium in highly acidic urine was more related to urinary pH than to systemic changes in acid-base balance.[1] This prompted us to investigate clearances of many weak organic acids and bases at the extremes of urinary pH, both in man and experimental animals. It soon became clear that many lipid-soluble drugs showed a pH-dependent excretion, but that in the case of water-soluble acids of the Krebs cycle, e.g., citric and a-ketoglutaric acids, it was systemic acidity and alkalinity which determined clearance rates.

"It seemed to us that the diffusion characteristics of the lipid-soluble compounds could easily be analysed mathematically even by individuals like ourselves who were relatively ignorant of advanced mathematical techniques. One of the main difficulties was that a somewhat naive and too literal application of diffusion theory gave the result that the clearance of a weak organic acid should increase ten-fold for every unit rise of urinary pH, whereas in most cases the observed rise was about ten-fold for every three units of increase of urinary pH. This discrepancy was satisfactorily explained by limiting factors, detailed in the abstract to the paper. Defects in the argument which have been resolved in later papers were that it was not sufficiently emphasized that diffusion was mainly in the direction of tubular fluid to pericapillary blood,[2] and that there was a fundamental difference in the mechanisms of diffusion of lipid soluble compounds, e.g., quinine, and predominantly water-soluble bases, e.g., ammonia.[3] The latter compounds have later been shown to diffuse through membrane pores and not through the bimolecular lipid layer of the tubule cells.

"In retrospect, the appeal of this article was that it allowed prediction of the type of excretion of weak organic acids and bases, and thus greatly facilitated subsequent research. The principles involved have later been applied to the stomach, intestine, pancreas, brain and cerebro-spinal fluid, and to individual cells. Diffusion into cell cytoplasm has stimulated use of partition methods in the measurement of intra-cellular pH, particularly by use of the weak acid dimethyloxazolidine-dione and the weak base nicotine. The appeal of the article may well have been that the mathematical methods involved were relatively simple, and falsely gave both the writers and readers the pleasant, if temporary, delusion that they understood something of mathematical reasoning."

1. **Ferguson E B, Jr.** A study of the regulation of the rate of urinary ammonia excretion in the rat. *J. Physiology* **112**:420-5, 1951.
2. **Weiner I M & Mudge G H.** Renal tubular mechanisms for excretion of organic acids and bases. *Amer. J. Med.* **36**:743-62, 1964.
3. **Bourkc E, Asatoor A M & Milne M D.** Mechanisms of excretion of some low-molecular weight bases in the rat. *Clin. Sci.* **42**:635-42, 1972.