This Week's Citation Classic®
CC/NUMBER 37
SEPTEMBER 16, 1985

Kunin C M. A guide to use of antibiotics in patients with renal disease: a table of recommended doses and factors governing serum levels.
Ann. Intern. Med. 67:151-8, 1967.
[Depts. Preventive Medicine and Medicine, Univ. Virginia Sch. Med., Charlottesville, VA]

This paper provides a table that describes the factors that determine persistence of antibiotics in the serum of patients with renal disease. It is based on concepts developed by the author and a review of the literature. It explains how to adjust the dosage in order to provide effective therapy with minimal toxicity. [The *SCI*® indicates that this paper has been cited in over 200 publications since 1967.]

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August 12, 1985

The fundamental work in this field was begun in 1957, 10 years before the publication of this review. I was a fellow in infectious diseases under Maxwell Finland at the Thorndike Memorial Laboratory, which at that time was part of the Harvard Unit at the Boston City Hospital. The work was done to answer a difficult clinical question raised by William Bush, a resident in medicine. He had a patient who required streptomycin for treatment of tuberculosis but had renal failure as well. Bush knew that streptomycin was excreted almost entirely by the kidneys and reasoned that the dose should be adjusted to prevent toxicity. He expected that since I was the infectious disease fellow, I should have the answer. I recommended that he reduce the dose. He replied, "How much?" I didn't know. I felt guilty and embarrassed by my ignorance and decided to try to search for an answer.

At that time, there were many people with renal failure at the Peter Bent Brigham Hospital, Boston, in John Merrill's unit. With his permission, I began to study all of the available antibiotics in these patients and in healthy volunteers. I gave an intravenous bolus of each drug to the subjects and drew blood specimens at periodic intervals thereafter. Anthony Glazko of Parke-Davis performed the chemical assays for chloramphenicol and explained to me the complex biotransformation of this drug.

A great deal of data were generated, but I had great difficulty in finding a way to express the information. Christopher Martin, my co-fellow, solved the problem by explaining to me the concept of "half-life in serum," which he had used in studying the persistence of immunoglobulins in patients with hypogammaglobulinemia. Sidney Ingbar taught me the principles of pharmacokinetics, which he was using to study thyroid function, and Rudi Schmid helped me interpret data on chloramphenicol, which is conjugated in the liver very much like bilirubin. The theoretical concept of this work was based on the mechanisms of clearance of mannitol by the kidney developed by Newman *et al.*[1] The advantage of working at the Thorndike lab was that there was a family atmosphere in which people with diverse interests shared their ideas freely. The unifying principles of biology and medicine did the rest.

The first three papers[2-4] were submitted to the *Journal of Clinical Investigation* and rejected. Finland, however, was aroused and asked for another review. The papers were finally accepted. The editor evidently feared Finland's wrath more than he doubted my ability.

I am somewhat surprised that this review paper has been cited more frequently than the initial reports. I suppose that the *Annals of Internal Medicine* has a wide readership. The field has expanded greatly and has been extended to virtually all drugs. The FDA requires pharmacokinetic studies of new drugs. One can now find recommendations for adjustment of dosage in renal and hepatic disease in the drug package inserts.

An overview of the use of antibiotics as an anti-infective agent is formalized in the work of Mandell, Douglas, and Bennett.[5]

1. **Newman E V, Bordley J, III & Winternitz J.** The interrelationships of glomerular filtration rate (mannitol clearance), extracellular fluid volume, surface area of the body, and plasma concentration of mannitol. A definition of extracellular fluid clearance determined by following plasma concentration after a single injection of mannitol. *Bull. Johns Hopkins Hosp.* 75:253-68, 1944. (Cited 85 times since 1955.)
2. **Kunin C M, Rees S B, Merrill J P & Finland M.** Persistence of antibiotics in blood of patients with acute renal failure. I. Tetracycline and chlortetracycline. *J. Clin. Invest.* 38:1487-97, 1959. (Cited 125 times.)
3. **Kunin C M, Glazko A J & Finland M.** Persistence of antibiotics in blood of patients with acute renal failure. II. Chloramphenicol and its metabolic products in the blood of patients with severe renal disease or hepatic cirrhosis. *J. Clin. Invest.* 38:1498-508, 1959. (Cited 185 times.)
4. **Kunin C M & Finland M.** Persistence of antibiotics in blood of patients with acute renal failure. III. Penicillin, streptomycin, erythromycin and kanamycin. *J. Clin. Invest.* 38:1509-19, 1959. (Cited 140 times.)
5. **Mandell G L, Douglas R G, Jr. & Bennett J E.** *Anti-infective therapy.* New York: Wiley, 1985. 516 p.

