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This Week's Citation Classic

Doherty J E. The clinical pharmacology of digitalis glycosides: a review.
Amer. J. Med. Sci. **255:**382-414, 1968.
[Univ. Arkansas Sch. Med., Dept. Med. & Med. Serv., Little Rock Vet. Admin. Hosp. Little Rock, AR]

The biologic half-times and pharmacokinetic behavior of the important digitalis glycosides are reviewed. Digoxin is excreted primarily in the urine as the unchanged glycoside and $T^{1/2}$ is prolonged by renal failure. Digitalis resistance is noted in thyrotoxicosis; sensitivity in myxedema, and pulmonary disease. A plea is made for smaller doses to avoid toxicity. [The *SCI*® indicates that this paper has been cited over 180 times since 1968.]

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"I was surprised to receive this invitation. This paper is a review. I suppose one of the major reasons it was so popular was because it was timely. This places most of the credit on Arnold Weissler, the editor of the *journal* at the time, who asked me to prepare the manuscript.

"The review was based upon a paper I read at an American Heart Association meeting a year or so before for a panel discussion on the digitalis glycosides. I suppose that one of the reasons for its 'citation' popularity was its emphasis on pharmacokinetics. It was the first review of digitalis to emphasize this discipline and to focus on the special contribution of the post World War II tracer isotope turnover studies to this part of clinical management of patients who required this medication. Digoxin was the fourth most frequently prescribed drug by physicians in 1971 and continues to be near the 'top-of-the-line' today.

"Our group in Little Rock was fortunate enough to have had a major role in these studies, having conceived and contracted for a tritium label of digoxin after earlier studies with tritiated cholesterol, a compound of similar chemical structure, demonstrated this was feasible.[1] The experience we gained: with this work assisted us in experimental design and techniques used in human tracer turnover studies essential to success of the experiments which led to publication and later to the review.

"I recall vividly the quiet excitement of the late Bill Perkins, my nuclear medicine associate, when we began this work. Ours was a small operation and the opportunity to 'scoop' was a very compelling reason to push ahead. We knew that studies with tritium labeled digoxin would provide significant new knowledge, immediately visible and important to the clinical use of this popular glycoside. We ultimately published about fifty papers related to tritiated digoxin, including this review.

"A review of clinical pharmacologic studies appeals to physician-readers because of the clinical application that is more often apparent in a review than in original publications. In addition, there is opportunity to link the more basic studies to clinical practice, as well as providing subsequent authors with a single reference, rather than multiple reference sources.

"Due credit is acknowledged and given to cooperative patients, dedicated technicians, house staff, professional associates, as well as our students, who continue to inspire us."

1. **Doherty J E, Perkins W H, Shapiro I & Dodd C.** Radiocarbon and tritium labeled cholesterol in alpha and beta lipoproteins after oral administration to human subjects. *J. Lab. Clin. Med.* **59:**550-7, 1962.