

# This Week's Citation Classic

CC/NUMBER 47  
NOVEMBER 19, 1979

**Smith T W, Butler V P, Jr. & Haber E.** Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. *New Eng. J. Med.* **281**:1212-6, 1969.  
[Dept. Med., Harvard Med. School; Cardiac Unit, Med. Service, Massachusetts General Hosp. Boston, MA; Dept. Med., Columbia Univ. Coll. Physicians and Surgeons, New York, NY]

**A rapid, sensitive, and specific radioimmunoassay for the cardiac glycoside digoxin is described. The assay was used to show that the mean serum digoxin concentration in a group of patients with cardiac arrhythmias due to digoxin toxicity was significantly greater than for patients without signs of toxicity. [The SC<sup>®</sup> indicates that this paper has been cited over 390 times since 1969.]**

Thomas W. Smith  
Department of Medicine  
Cardiovascular Division  
Peter Bent Brigham Hospital  
Boston, MA 02115

August 3, 1979

"Like many previous 'Citation Classics,' this paper is frequently cited because it described a convenient method that has come into common laboratory use. The groundwork for this contribution was laid by the studies of Vincent Butler,<sup>1</sup> who applied approaches developed by Erlanger and Beiser<sup>2</sup> to the problem of eliciting digoxin-specific antibodies, and by further work<sup>3</sup> in our laboratory characterizing these high-affinity antibody populations.<sup>3</sup> Because of a wealth of immunologic expertise and experience with angiotensin radioimmunoassays, the laboratory of Edgar Haber was an ideal environment in which to combine the several concepts and techniques used in the development of the digoxin radioimmunoassay. The close and continuing collaboration in these and related studies among the laboratories of Haber, Butler, and myself remains a source of stimulation and satisfaction.

"An unusual feature of the project was the fact that it was undertaken in my spare time while in training as a clinical fellow in the cardiac catheterization laboratory, with the encouragement of Charles A. Sanders, then director of the laboratory. One hopes that clinical training programs of the future will continue to provide this sort of flexibility.

"The general conclusions of the paper, that serum digoxin concentrations could be measured accurately and conveniently and that mean concentrations are higher in digoxintoxic patients than in those without toxicity, have been confirmed in at least 30 sub-sequent published studies. It has also been confirmed that overlap in levels is seen among patients with and without evidence of toxicity. We cautioned then as now that serum digoxin concentrations must be interpreted in the clinical context and weighed together with other factors that influence the response of the individual patient. As might have been expected, the wide-spread availability of a convenient assay procedure not requiring administration of radioactively labeled sub-stances to patients facilitated clinical studies of digoxin pharmacokinetics.

"In retrospect, one of the most important concepts arising from this work was the recognition that antibody populations of sufficient specificity and affinity allow the measurement of minute concentrations of drugs and endogenous substances in biological fluids without prior separation procedures. Also of importance has been the recognition that antibody populations directed against a non-antigenic drug molecule coupled as a hapten to a carrier macromolecule frequently achieve affinity constants of  $10^{10} \text{ M}^{-1}$  or greater. Purified Fab fragments of these antibodies have now been used clinically to reverse otherwise fatal, advanced digoxin intoxication."<sup>4</sup>

1. **Butler V P, Jr. & Chen J P.** Digoxin-specific antibodies. *Proc. Nat. Acad. Sci. US* **57**:71-8, 1967.
2. **Erlanger B F & Beiser S M.** Antibodies specific for ribonucleosides and ribonucleotides and their reaction with DNA. *Proc. Nat. Acad. Sci. US* **52**:68-74, 1964.
3. **Smith T W, Butler V P, Jr. & Haber E.** Characterization of antibodies of high affinity and specificity for the digitalis glycoside digoxin. *Biochemistry* **9**:331-7, 1970.
4. **Smith T W, Haber E, Yeatman L & Butler V P, Jr.** Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *New Eng. J. Med.* **294**:797-800, 1976.