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Wilkinson G R & Shand D G. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* 18;377-90, 1975. [Department of Pharmacology, Vanderbilt University, Nashville, TN]

This paper described a pharmacokinetic model for the hepatic elimination of drugs based on the relationship between the involved physiological factors including the new concept of "intrinsic clearance." It was shown that such a unifying model could describe the known effects of perturbations in the determinants on a drug's blood concentration-time profile caused by disease-states, drug interactions, interindividual variability in drug metabolizing ability, and route of administration. A generalizable classification was developed that allowed prediction of in vivo disposition characteristics according to the particular drug's intrinsic clearance. [The *SCI*® indicates that this paper has been cited in more than 1,335 publications, making it the most-cited paper published in this journal]

Physiological Model of Drug Clearance

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The genesis of this "commentary" began shortly after I joined the clinical pharmacology group at Vanderbilt in 1971. David Shand had some unusual data concerning the oral first-pass elimination of propranolol that could not be described by the then-available pharmacokinetic models. Stimulated by the recent seminal work of Ken Blschoff and Bob Dedrick, I subsequently developed a physiologically based model of the liver for this purpose. The biological determinants of tissue uptake and their relationships with those of drug metabolism were a central feature of this model. By contrast, a simpler model was independently developed around the same time by Malcolm Rowland and his colleagues at the University of California, San Francisco, which again emphasized the Important role of blood flow and, in this case, its relationship to a nonphysiologically defined capacity of the liver for drug elimination. Combination of the two modeling approaches led to the development of the concept of "intrinsic clearance" and the "well-stirred" model of organ clearance. Subsequent model testing and validation involved the experimental expertise and enthusiastic collaboration of Alan Nies and Bob Branch.

The model has been widely accepted and applied, particularly to whole body pharmacokinetic studies describing the blood/plasma concentration-time profile of drugs metabolized by the liver. Several factors probably contributed to such extensive application. Most importantly, the model provided a general and unifying approach, integrating both a drug's inherent ability to be eliminated and the body's physiology—the "black box" suddenly became of considerably lighter hue and broad principles became apparent. Moreover, the model was mathematically simple, since only basic arithmetic operations were involved, and there was also a degree of scientific elegance—it felt intuitively correct. Because of the model's simplicity and intuitiveness, I had some initial difficulty in persuading David that writing this commentary would, in fact, be contributory. Timing was also Important since the limitations of the widely applied compartmental approach beyond phenomenological description were beginning to be recognized. Salesmanship was another factor—there were frequent national and international opportunities to publish and verbally present the resulting research to the broad and diverse audience involved in the development, evaluation, and therapeutic use of drugs.

The research was supported by a National Institute of General Medical Sciences center grant with John Oates as principal investigator. This combination provided an ideal nurturing environment for young scientists to develop, to interact, and to share their disparate but complementary talents and efforts. Also, we were largely shielded from the vicissitudes associated with obtaining adequate grant support and other nonresearch issues that could have distracted us from the fun and excitement of our discoveries. In fact, none of the original research or its resulting applications were ever described in a National Institutes of Health application or underwent peer review.

For several years afterwards, the group continued to apply the model to a variety of problems related to human drug disposition. But, once the general principles had been established and entered the dogma,[1] our interests turned to other areas. Others have, however, continued to model the liver with particular focus on events within the organ—a situation where the "well-stirred" model begins to break down. This has led to the development of several alternative and much more complex models that attempt to account for the marked heterogeneity of hepatic structure and function.[2-4] This is a formidable challenge, and no single universal model has yet to be described at this organizational level.

1. **Wilkinson** G **R.** Clearance approaches in pharmacology. *Pharmacol Rev.* 39:**1** -47, **1**987.
2. **Rlvory K P, Roberts M S & Pond** S **M.** Axial tissue diffusion can account for the disparity between current models of hepatic elimination for lipophilic drugs. *J. Pharmacok. Biopharm.* 20:19-61, 1992.
3 **Saville B A, Gray M R 4 Tam Y K.** Models of hepatic dmg elimination. *Drug Metab. Rev.* 24:49-88, 1992. **4. St-Plerre M V, Lee P I & Pang K** S. A comparative investigation of hepatic clearance models: predictions of metabolite formation and elimination. *J. Pharmacok. Biopharm.* 20:105-45, 1992.

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