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 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.

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