Introduction

This book is the second in a series sponsored by the Esteve Foundation exploring "... seminal articles in the development ... of different aspects of pharmacotherapy" [1]. Our principal goal in preparing this text was to select approximately 30 articles which have made exceptional contributions to the enormous progress in pharmacokinetics. Furthermore, clinical pharmacokinetics was chosen for special emphasis. We have divided these contributions into those which predate 1950, and by decade thereafter. We occasionally made an accommodation for superior content and literary style. Thus, though the paper by Price Evans *et al.*[2] is not the first to suggest the genetic control of acetylation in man, it is superb reading, it meticulously cites the contribution of others and it goes on to report observations of isoniazid acetylation in about 500 subjects. Forty years after the study was performed, it is still arguably one of the best pharmacogenetic papers ever published. With regard to our chronological approach, we believe that students and investigators will benefit from viewing the logical progression of this discipline and will better appreciate how we have all benefited from "standing on the shoulders of giants".

With regard to the earliest seminal publication in clinical pharmacokinetics, it is our opinion that honor should be bestowed on Harry Gold or more precisely on the work he published in 1929 with Arthur DeGraff[3]. It should be noted that these authors, using only careful pharmacodynamic monitoring in patients with "auricular fibrillation", correctly deduced that the elimination of digitalis was a first order process (see their Summary and Conclusion section). This warrants special note because their study was, out of necessity, performed using "Compressed tablets of dried digitalis leaf standardized by the cat unit method ...".

Many investigators[4] realized that studying ester anesthetics could provide insights into significant aspects of drug disposition and clinical pharmacology. However, it seems appropriate to be awed by the work of Goldberg *et al.*[5], who reported in 1943 that procaine was metabolized by an enzyme in human blood (but not dog blood), that this enzyme formed *p*-aminobenzoic

acid (PABA), that PABA was further biotransformed to an acylated product (*N*-acetyl-PABA), that human liver was also an important source of esterasic activity, that absorption into blood following spinal injection of procaine was principally responsible for termination of anesthetic effect, and that almost the entire dose could be recovered as metabolites in urine. Finally, in this early period, Shannon *et al.*[6] published "The pharmacological basis for the rational use of atabrine in the treatment of malaria"(1944). This article provides a detailed basis for "loading doses", explores drug accumulation kinetics, recognizes that a large volume of distribution mandates slow elimination (*i.e.,* a long half-life), and suggests that drug concentration in plasma water is "equal to that of extracellular fluid and is the equilibrium concentration of the body as a whole". At the same time, and a few miles away, Smull *et al.*[7] elegantly documented that high dose bicarbonate therapy used to improve the tolerability of high dose salicylate treatment, typically caused a 50% decrease in serum salicylate level. Indeed, all of the findings discussed above were made with primitive analytical instrumentation, but these methods were often supplemented with ingenious approaches to validate analytical procedures and hence, these observations have withstood the test of time. Significantly, all this work was achieved many years before Dost[8] introduced the term pharmacokinetics[9].

Much of the progress made in pharmacokinetics during the 1950s was based on contributions from Bernard B. Brodie's Laboratory of Chemical Pharmacology at the National Institutes of Health[10-14]. The principal area of this progress was in establishing the mechanisms underlying observations made *in vivo*. Many of these investigations concerned the factors modulating the processes of drug absorption, distribution and elimination as they influenced pharmacologic effect. The rate of absorption from the intestine was found to be highly dependent upon the lipid-solubility of its unionized form of the drug[13]. Distribution into the central nervous system was recognized as typically being controlled by simple diffusion, and the determinants to this process were found to be physicochemical parameters, such as the dissociation constant and lipid-solubility of the unionized form of the drug[14]. Many aspects of the cytochrome P450 system were being elucidated. For example, it was reported that metabolic transformations occur in the microsomes and this process required the presence of the soluble fraction and oxygen. Furthermore, it was demonstrated that interspecies differences in drug response were largely explained by differences in metabolism[11,12], and that occasionally extrahepatic metabolism played a major role in determining the pharmacologic and/or toxicologic effect. Efforts to foster more rational drug use flourished. The availability of better analytical methods allowed the correlation of effect with the plasma concentration of drug. For example, it is noteworthy that Truitt *et al.*[15] suggested that the minimally effective and toxic plasma concentrations of theophylline were 5 and 16 µg/ml, respec-

tively. This proposal, made in 1950, was based on the detailed examination of the time course of the diuretic and untoward effects associated with various routes of administration. Using techniques such as counter-current distribution, it was determined that in man, approximately 50% of a dose of theophylline was biotransformed to 1,3-dimethyluric acid[10]. In parallel to this analytical progress (*e.g.,* the first review of gas liquid chromatographic techniques was published in 1959, see ref. 16), well designed studies (placebo controlled, cross-over, double-blind, randomized studies) often allowed elegant and accurate therapeutic conclusions by measuring multiple response parameters for a drug. An excellent example is the study by Seed *et al.*[17], who reported that morphine was about sevenfold more potent than dihydrocodeine, and that at equianalgesic doses both drugs elicited very similar side effects, including respiratory depression. Another example is illustrated by the pioneering pharmacogenetic study of Kalow and Gunn[18], who measured apnea as a function of succinylcholine dose and simultaneously evaluated the serum cholinesterase activity in patients. This study lead to the conclusion that serum cholinesterase activity was a hereditary trait.

The principal pharmacokinetic advances made in the 1960s were the recognition that drug disposition was often under strong environmental[19,20] or genetic[2] control, and that mathematical modeling often allowed accurate prediction of plasma concentration of drug/metabolite and occasionally of pharmacologic effect[21]. Furthermore, the first rigorous approach to assess the process of drug absorption was published[22]. Among environmental factors, compounds such as phenobarbital were shown to be potent enzyme inducers that caused profound reduction of drug levels and effect (in rats a 95% decrease in hexobarbital sleep time and a 98% reduction in the duration of zoxazolamine paralysis). Indeed, these studies and the observation that many drugs were competitive inhibitors of one another's metabolism[23], provided the basis for a rational search for significant drug interactions. Of note, it was recognized that this selectivity of inhibition/induction strongly suggested multiple forms of cytochrome P450 (*i.e.*, isozymes). For example, Conney *et al.*[19] demonstrated in 1960 that phenobarbital pretreatment caused a four- to fivefold increase in the rate of microsomal metabolism of hexobarbital and zoxazolamine, while benzo(a)pyrene pretreatment had a profound effect on zoxazolamine metabolism (fivefold) and no effect on hexobarbital metabolism. These observations in animals were confirmed in man with substrates such as dicumarol and phenytoin[20]. Specifically, Cucinell *et al.*[20] reported that phenobarbital pretreatment caused a significant decrease in the plasma levels of dicumarol which was associated with a diminished anticoagulant response. Furthermore, they reported that phenytoin plasma levels were halved by concurrent phenobarbital administration. Indeed, as discussed earlier, Price Evans *et al.*[2] provided compelling evidence for the strong genetic control of acetylation but commented that "variability in the plasma isoni-

azid concentration due to variations in weight indicates another component in the variances of the distribution curves for the two phenotypes", that is, the significant contribution of a nongenetic (*i.e.,* environmental) factor.

The final area in pharmacokinetics which began to bloom in the 1960s was the appreciation that rather complicated processes such as the time-course of pharmacologic effect[21] and drug absorption from the intestine[22] could be adequately described by relatively simple equations. Thus, it could be practical to predict such things as the duration and intensity of effects or the therapeutic consequences of changes in routes of administration. Indeed, shortly after this decade ended, truly comprehensive pharmacokinetic modeling was conducted for a number of antineoplastic agents with some notable success[24]. All of these contributions clearly moved us much closer to our current view of the utility of pharmacokinetic principles.

An abundance of data was now available which allowed the 1970s to be characterized by the revision and application of this knowledge to clinical practice. In addition, the search to identify the precise physiologic (hepatic blood flow, renal blood flow, etc.) and biochemical (intrinsic hepatic clearance, free fraction in plasma and tissue, etc.) factors which define the pharmacokinetics of a drug substantially advanced. More efficient and specific analytical techniques allowed routine therapeutic drug monitoring and this became a common clinical practice[25]. Drug plasma and tissue protein binding and the distribution of drugs attracted much attention. Gibaldi *et al.*[26,27] described in relatively simple terms the relationship between the pharmacodynamics (*i.e.,* onset, intensity and duration of effect), and the pharmacokinetics (*i.e.,* half-life and distribution) of a drug. Furthermore, the consequences of disease on the binding of drugs to plasma proteins is remarkably well described in the articles by Reidenberg *et al.*[28] and Piafsky and Borgå[29]. Specifically, the effect of renal failure on the binding of acidic drugs to albumin and the discovery that α_1-acid glycoprotein often controlled the binding of basic drugs in plasma greatly improved our understanding of this biochemical variable. The therapeutic utility of drug binding to proteins in plasma was established by Smith *et al.*[30] with the use of high affinity/high specificity/low molecular weight (eliminated by glomerular filtration) antibodies to digoxin, which allowed the rapid reversal of the toxic effects of this drug, even in cases of massive overdosage.

Having now studied plasma protein binding, the perfusion of clearing organs, and detailing the genetic and environmental control of the cytochrome P450 system, it was practical to integrate these independent variables and to identify an equation which accurately defined the relative importance of each variable in determining the clearance of a drug. Our understanding was improved enormously with the report of Wilkinson and Shand[31]. Stated

simply, this approach provided a practical and simple tool to reliably predict the changes in pharmacokinetics which should result from alterations in environmental factors, from changes in physiology, from the presence of disease or the coadministration of other drugs. An intriguing observation was reported two years later by Melander *et al.*[32]. Food substantially diminished the first-pass metabolism of propranolol and metoprolol, an observation that opened new areas of research which has lead to numerous drug-nutrition interaction studies. The same year, the existence of a wide variation in hypotensive response to debrisoquine prompted Mahgoub's group[33] to study the rate of hydroxylation of debrisoquine. They clearly showed the presence of a bimodal distribution which looked remarkably like an exaggerated version of that observed 20 years earlier with isoniazid (nonmetabolizer phenotype was due to homozygosity of an autosomal recessive allele; compare Figure 2 from reference 2 with Figure 2 in reference 33). Shortly afterward, investigators at Vanderbilt documented the profound stereospecificity of mephenytoin kinetics using elegant classical approaches[34]. This work lead to the demonstration of the pharmacogenetic control of this metabolic process[35,36].

At the University of California at San Francisco, Sheiner *et al.*[37] made another important contribution toward obtaining relevant estimates of pharmacokinetic parameters using sparse data sets such as those available from routine therapeutic monitoring. This approach is widely used and has contributed to more precisely define the kinetics of drugs in patient populations. Early in the 1980s, Holford and Sheiner published a highly readable paper[38] examining a variety of factors which can be involved in the linkage of pharmacokinetics and pharmacodynamics. A principal point made by these investigators was that even if the relationship between response and drug concentration is complex, (*i.e.,* indirect effects influenced by active homeostatic mechanisms such as hypotensive effects) an adequate model can usually be defined. Indeed, there are many groups attempting to use this approach to develop new chemical entities.

In conclusion, we apologize to those investigators who have made outstanding contributions to pharmacokinetics but whose work is not cited. It should be understood that we had to work within the length limitations of this book, meaning that on average we could include one paper for every two years starting from the pioneering work of Gold and DeGraff[3]. Obviously, this was a severe limitation. We do however offer one final acknowledgement. The faculty and trainees (post doctoral fellows and graduate students) from a relatively small number of institutions, most notably the University of California at San Francisco, SUNY/Buffalo, Vanderbilt, the University of Michigan, the University of Kentucky, the University of Kansas Medical Center, the Karolinska Institute, and the University of London School of

Pharmacy, have provided an enormous portion of the world's pharmacokineticists and they are to be congratulated for their contributions to this intellectually stimulating and exquisitely practical discipline. It should also be noted that a second apology could be provided to the authors of numerous more recent publications for the absence of their papers. We could easily have speculated regarding which recent publications will be recognized as "seminal" in the future, but our decision was to focus on a group of truly exceptional classic texts. We believe the reader will ultimately agree with us.

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